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Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.01/D12

Topic: A.01. Neurogenesis and Gliogenesis

Title: CHCHD2 is a critical regulator of adult hippocampal neurogenesis and neuronal maturation

Authors: *M. A. SIERRA-VELAZQUEZ, N. STEWART, J. SONG;
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Abstract: Adult Hippocampal Neurogenesis (AHN) is a highly regulated process wherein neural stem cells (NSCs) undergo fate decisions that balance self-renewal and differentiation. NSCs exhibit stage-dependent metabolic shifts toward mitochondrial oxidative phosphorylation (OXPHOS) upon cell-cycle entry and differentiation. Preliminary single-cell RNA sequencing revealed that coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), a regulator of OXPHOS and mitochondrial homeostasis, undergoes progressive downregulation during neurogenic differentiation despite the stage-dependent shift toward OXPHOS. This study aims to elucidate the necessity of CHCHD2 during physiological AHN. A tamoxifen-inducible triple-transgenic model (Ascl1CreERT2:CHCHD2^fl/fl:R26^tdTomato) was used in adult male and female mice to selectively excise CHCHD2 in active NSCs (aNSCs) and track neurogenic lineage progression. Coronal dentate gyrus sections were collected at defined neurogenic time points (7, 14, and 32 days post injection [dpi]). Stage-specific lineage progression was assessed through Ki67+ proliferating cells, Sox2+ glial progenitors, Tbr2+ neurogenic progenitors, DCX+ immature neurons, and NeuN+ mature neurons, while cellular morphology was quantified through radial process length, dendritic complexity, and dendritic spine density. Lineage progression and morphological analyses were performed in separate cohorts (n=5 and n=6 mice/genotype, respectively). At 7 dpi, CHCHD2 conditional knockout (cKO) in aNSCs significantly increased proliferative activity and immature neuron populations. Reductions in NSC radial process length further suggest an altered neurogenic lineage progression despite unchanged neurogenic progenitor populations. At 14 dpi, CHCHD2 cKO immature adult born neurons (ABNs) exhibited reduced dendritic complexity, indicating impaired structural maturation and a diminished capacity to integrate into existing hippocampal circuitry. By 32 dpi, CHCHD2 cKO ABNs displayed elevated dendritic spine density and increased Cleaved Caspase-3+ ABNs, suggesting altered synaptic remodeling accompanied by elevated cell death. These findings indicate that the early alterations in neurogenic lineage progression observed following CHCHD2 cKO are not maintained through later stages of neuronal maturation. Together, CHCHD2 is required for proper neurogenic lineage progression, neuronal maturation, and long-term survival of ABNs. CHCHD2 may therefore serve as a potential regulator linking mitochondrial homeostasis to NSC fate decisions in the adult hippocampus.

Disclosures: M.A. Sierra-Velazquez: None. **N. Stewart:** None. **J. Song:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.02/D13

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSERC Discovery Grant (400555)

Title: Assessing the Role of Adaptor Protein ShcD in Adult Neurogenesis and Affective Behavior

Authors: *H. YANG[1], B. ALURAL[2], C. CLAUSEN[3], N. JONES[4];
[2]Mol. and Cell. Biol., [1]Univ. of Guelph, Guelph, ON, Canada; [3]Univ. of Guelph, GUELPH, ON, Canada; [4]Guelph, ON.

Abstract: Olfactory dysfunction is increasingly recognized as a feature of neuropsychiatric disorders, including depression and anxiety, where alterations in sensory processing and neuroplasticity are observed. The olfactory system is uniquely positioned at the intersection of sensory function and adult neurogenesis, as it remains one of the few brain niches to undergo continuous neuronal renewal. Newly generated neurons from the subventricular zone migrate to the olfactory bulb and integrate into existing circuits that influence odor discrimination. Disruption to this tightly regulated process has been implicated in mood-related phenotypes. Our protein of interest, ShcD is the least characterized member of the Shc family that is involved in the signaling cascade of pathways downstream of receptor tyrosine kinases. ShcD knockout mice exhibited altered olfactory bulb morphology and impaired olfaction. Given the anatomical and functional connections between the olfactory system and limbic structures, perturbations in olfactory neurogenesis may represent a critical but underexplored mechanism contributing to affective dysfunction.

Based on its putative involvement in neuronal development, ShcD is hypothesized to influence adult neurogenesis within the olfactory system, thereby contributing to alterations in olfactory function and anxiety/depression-like behaviours. In our preliminary results, ShcD expression is the highest when the NSCs are becoming immature neurons. When ShcD is overexpressed, more cells exited the cell cycle and showed premature differentiation. In behaviour tests, ShcD KO mice are seen to have altered baseline response to stressful environments, with possible sex differences. Furthermore, primary cells were successfully derived from adult neurogenic niche of ShcD WT/KO mice, showing promising putative results.

The purpose of this research is to investigate the role ShcD plays in neuronal maturation and behaviour through in vitro and in vivo models. By integrating behavioral, cellular, and molecular approaches, this work aims to investigate how disruptions in adult neurogenesis influence olfactory function and neurobehavioral outcomes relevant to anxiety and depression.

Disclosures: H. Yang: None. **B. Alural:** None. **C. Clausen:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.03/D14

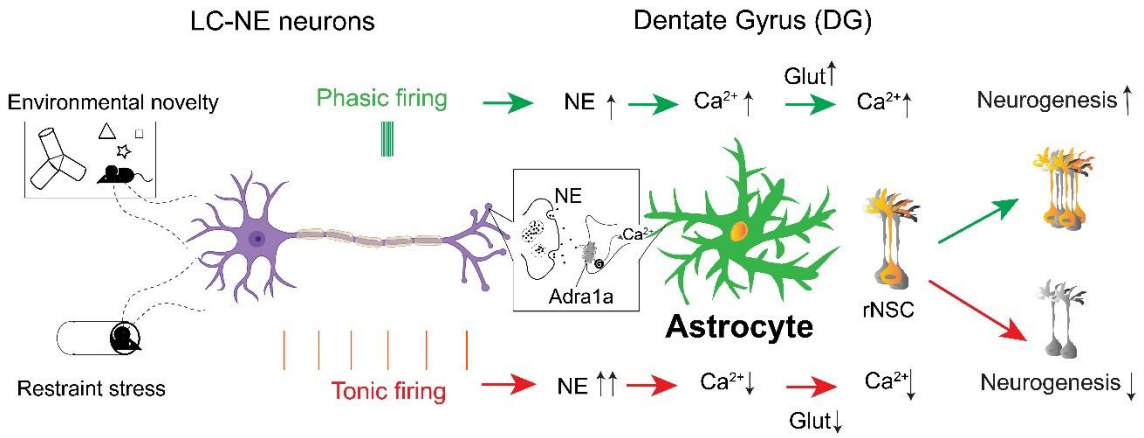
Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01 MH122692
NIH R01 MH132222

Title: Experience-Dependent Locus Coeruleus Firing Patterns Bidirectionally Regulate Adult Neurogenesis through Astrocytic Signaling

Authors: *Z. CHEN[1], B. ASRICAN[2], D. MELVILLE[2], K. VALENTINE[2], W. T. FARMER[2], J. SONG[2];
[1]Univ. of North Carolina Chapel Hill, Chapel hill, NC; [2]Pharmacol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Adult neural stem cells (NSCs) in the dentate gyrus (DG) are regulated by environmental experiences, but the underlying circuit mechanisms remain unclear. Using in vivo multichannel recording, fiber photometry, two-photon calcium imaging, optogenetics, and cell type-specific genetic manipulations, we examined how environmental novelty (EN) and restraint stress (RS) regulate NSC activity and proliferation. EN increased NSC calcium activity and proliferation, whereas RS decreased both. Among DG afferent populations, DG-projecting locus coeruleus (LC) neurons showed the strongest activation during both EN and RS. In vivo multichannel recording revealed that EN and RS elicited distinct firing patterns in DG-projecting LC neurons, producing different norepinephrine (NE) dynamics in the DG. Optogenetic stimulation demonstrated that phasic LC-DG activity enhanced NSC activity and proliferation, whereas tonic LC-DG activity suppressed them. Cell type-specific fiber photometry and optogenetic manipulations identified astrocytes as a key intermediary. Phasic NE signalling increased astrocytic calcium activity and glutamatergic signalling, whereas tonic NE signalling induced a transient increase followed by prolonged suppression of astrocytic activity, resulting in reduced glutamate release. Astrocyte-specific disruption of α1A-adrenergic receptor (Adra1a) signalling or downstream Gq signalling abolished EN- and phasic LC-DG stimulation-induced increases in NSC activity and proliferation, and prevented the suppression induced by RS- and tonic LC-DG stimulation. These findings identify an LC-DG astrocyte-NSC pathway through which distinct LC firing patterns translate experiential states into bidirectional regulation of adult neurogenesis.



Disclosures: Z. Chen: None. **B. Asrican:** None. **D. Melville:** None. **K. Valentine:** None. **W.T. Farmer:** None. **J. Song:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.04/D15

Topic: A.01. Neurogenesis and Gliogenesis

Support: JSPS KAKENHI Grant Number 22K11528
JSPS KAKENHI Grant Number 25K03022
JSPS KAKENHI Grant Number 25KJ1999
The Nakatomi Foundation research grant

Title: Elucidating the molecular mechanisms by which exercise-induced hippocampal cell proliferation is inhibited by antioxidant supplements

Authors: *H. ONISHI[1,2], R. TSUCHIDA[1,2], J. TAGAMI[1], R. MURATA[1], T. SAITO[1], R.-U. TAKAHASHI[3], T. MIYAMOTO[4], T. NISHIJIMA[1];
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Abstract: [Background] Exercise is attracting attention as a therapeutic strategy for hippocampal dysfunction, including Alzheimer's disease and depression, and its beneficial effects are thought to be partly mediated by enhanced hippocampal neurogenesis. Therefore, understanding how exercise promotes hippocampal neurogenesis is crucial. Our previous study focused on antioxidants because exercise requires large amounts of ATP and concomitantly generates reactive oxygen species (ROS) as byproducts. Previous studies have suggested beneficial effects

of antioxidants on hippocampal function. Taken together, we hypothesized that antioxidant intake during exercise would synergistically enhance hippocampal neurogenesis. Unexpectedly, we found that exercise-induced hippocampal neurogenesis was suppressed by administration of the vitamin C (VC) and vitamin E (VE) mixture. To explain this effect, we focused on the concept of mitohormesis, which suggests that appropriate ROS levels are essential for physiological adaptation, whereas excessive ROS levels induce cellular damage. However, it is unclear whether exercise-induced hippocampal neurogenesis is regulated by mitohormesis. [Purpose] This study aimed to determine whether exercise-induced hippocampal cell proliferation can be explained by mitohormesis and to elucidate the molecular mechanisms. [Methods] Ten-week-old male C57BL/6J mice were subjected to voluntary exercise for 5 days. To assess whether VC or VE inhibited exercise-induced cell proliferation, mice received vehicle, VC or VE once daily and were intraperitoneally injected with 100 mg/kg BrdU on day 5. Hippocampal cell proliferation was evaluated by BrdU immunohistochemistry (IHC). Next, to reveal molecular mechanisms, an additional experiment was conducted using the same protocol. The hippocampi were collected separately from the left and right hemispheres for IHC and RNA sequencing, respectively. Total RNA was extracted from the right hippocampus. [Results] We found that exercise-induced hippocampal cell proliferation was inhibited by VE, but not by VC. Interestingly, no significant changes were observed in basal cell proliferation. Next, to identify genes, we compared hippocampal gene expression profiles between the Ex + Veh and Ex + VE groups using bulk RNA sequencing and identified a novel candidate gene potentially involved in the regulation of exercise-induced hippocampal cell proliferation. [Conclusion] These findings suggest that exercise-induced hippocampal neurogenesis may be regulated by mitohormesis and identify a novel candidate gene potentially involved in this molecular mechanism.

Disclosures: H. Onishi: None. **R. Tsuchida:** None. **J. Tagami:** None. **R. Murata:** None. **T. Saito:** None. **R. Takahashi:** None. **T. Miyamoto:** None. **T. Nishijima:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.05/D16

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIDCD R01DC018516
NIGMS T32GM144300

Title: Impact of Methimazole-Mediated Olfactory Sensory Neuron Ablation on Subventricular Zone Neurogenesis in Male and Female Mice

Authors: *S. C. SWEAT[1], M. RODRIGUEZ[2], C. E. CHEETHAM[3];
[1]Univ. of Pittsburgh/Carnegie Mellon Univ. Med. Scientist Training Program, Pittsburgh, PA; [3]Dept. of Neurobio., [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The rodent olfactory system, a highly dynamic and plastic system, benefits from lifelong neurogenesis in both the olfactory epithelium (OE) and the subventricular zone (SVZ). Olfactory sensory neurons (OSNs) in the OE project their axons to the olfactory bulb (OB) to provide odor input. SVZ-derived interneurons migrate via the rostral migratory stream (RMS) to the OB in order to integrate into existing circuitry. This ongoing neurogenesis allows for significant plasticity within the OB circuitry, which is critical in adaptive responses to environmental stimuli. While SVZ neurogenesis is known to be regulated by a variety of external stimuli, the effects of OE injury on SVZ neurogenesis, which may be modulated to maintain homeostasis of OB circuitry, are not well understood. Methimazole (MMZ) chemically ablates OSNs, causing cell death while sparing OE stem cells such that regeneration of OSNs and reinnervation of the OB is possible. A recent study [PMID: 38522356] observed a decreased density of newborn (EdU+) cells in the OB 3 days post-MMZ injection followed by an increase at 7 days post-MMZ, compared to controls. However, the effect of MMZ-mediated OSN ablation on SVZ neurogenesis, specifically neuroblast proliferation, remains unknown. Using male and female 10-week-old C57BL/6J mice, we quantified SVZ neurogenesis 1, 7, or 21 days after injection of EdU and either saline (vehicle control) or MMZ. OB sections and brain sections containing SVZ underwent EdU staining and labeled cells were imaged with widefield microscopy and counted. We observed a similar density of EdU+ cells in the OB granule cell and glomerular layers regardless of saline or MMZ treatment in both male and female subjects. Interestingly, in the SVZ, at the 1-day time point, MMZ-treated males showed significantly higher (Two way ANOVA w/ Tukey post hoc; adjusted p-value = 0.0269) EdU+ cell density (mean = 69.6608, SD = 11.157) compared to saline-treated males (mean = 44.9181, SD = 11.933). In contrast, females at this time point showed similar (Two way ANOVA w/ Tukey post hoc; adjusted p-value = 0.8761) SVZ EdU+ cell density whether treated with MMZ (mean = 35.8398, SD = 31.971) or saline (mean = 37.4531, SD = 13.387). These results suggest that MMZ-mediated OSN ablation affects SVZ neurogenesis in male mice as early as 1 day post injection and lay a foundation for further exploration of sex differences in SVZ neurogenesis in post-injury models.

Disclosures: S.C. Sweat: None. **M. Rodriguez:** None. **C.E. Cheetham:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.06/D17

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH 5T32 NS077889
Kentucky Spinal Cord and Head Injury Research Trust grants 19-5A and 23-12

Title: Neurogenesis and Long-term Proliferative Capacity are Maintained in the Neurogenic Niche of the Hippocampus after Traumatic Brain Injury

Authors: *J. G. BARNES[1,2], Z. DEGRAFF[1], C. HELTON[1,4], K. BROWN[1,4], M. C. JONES[1], K. E. SAATMAN[1,2,3];
[1]Univ. of Kentucky Spinal Cord and Brain Injury Res. Ctr., Lexington, KY; [2]Dept. of Neurosci., [3]Dept. of Physiol., Univ. of Kentucky Col. of Med., Lexington, KY; [4]Univ. of Kentucky Col. of Arts and Sci., Lexington, KY

Abstract: Traumatic brain injury (TBI) induces acute neuronal death in the hippocampal dentate gyrus, a structure critical for learning and memory. An early increase in proliferation of neural stem and progenitor cells (NSCs/NPCs) within the dentate gyrus subgranular zone has been linked to increased neurogenesis and cognitive recovery following injury but could compromise long-term neurogenic capacity. To investigate chronic post-traumatic neurogenesis and neurogenic capacity in both sexes, an inducible reporter mouse model ($Ascl1^{CreERT2/+}$ x $R26Rtd^{Tom/tdTom}$) was used to label and trace the fate of Ascl1+ cells. Ascl1+ cells include type-2a NPCs and activated radial glial-like stem cells (RGLCs). TdTomato expression was induced 6 weeks after mice received a controlled cortical impact (CCI) (n=10/sex) or sham (n=8/sex) injury. At 12 weeks post-injury, ample time for labeled NPCs to reach neuronal maturity, numbers of tdTomato+ cells were counted and found to be equivalent in CCI and sham controls ($p=0.414$, main effect: injury), indicating no net change in neurogenesis. Approximately 15-20% of tdTomato-labeled cells were proliferating 6 weeks after induction. While there was a slight decrease in the hippocampus ipsilateral to the surgery as compared to contralateral ($p=0.015$, main effect: hemisphere), there were no differences based on injury or sex. However, the small subset of tdTomato+ cells that maintained RGLC morphology was reduced for both sexes in the ipsilateral hippocampus after CCI ($p=0.0142$, interaction: injury x hemisphere). These results could indicate that fewer activated RGLCs were labeled at 6 weeks or that symmetric division of RGLCs increased between 6 and 12 weeks in the injured hemisphere. Neurogenic capacity, assessed through counts of proliferating (MCM2+) cells in the neurogenic niche, activated RGLCs (MCM2+/Nestin+), and neuroblasts/immature neurons (DCX+), was not diminished at 12 weeks post-injury ($p= 0.8953$, $p=0.338$, $p= 0.230$, respectively, main effect: injury). In conclusion, labeled NSCs/NPCs at 6 weeks after injury gave rise to equivalent numbers of cells surviving to 12 weeks and neurogenic capacity was maintained at this late time point, suggesting that early posttraumatic neurogenic plasticity does not compromise chronic neurogenic capacity.

Disclosures: J.G. Barnes: None. **Z. DeGraff:** None. **C. Helton:** None. **K. Brown:** None. **M.C. Jones:** None. **K.E. Saatman:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.07/D18

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01NS107370
R01NS121316

Title: tDCS Restores Hippocampal Cell Proliferation and Promotes Neuronal Differentiation in the TBI Brain

Authors: *S. G. HANEY, D. GONDALIA, J. Y. SU, B. S. MAIN, J. D. O'LEARY, M. P. BURNS;
Neurosci., Georgetown Univ., Washington, DC

Abstract: Adult hippocampal neurogenesis in the dentate gyrus is critical for learning and memory recovery following traumatic brain injury (TBI), yet the chronic post-injury environment suppresses cellular proliferation and survival. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory intervention that promotes neuroplasticity, but its capacity to restore neurogenic potential in the chronic TBI setting remains poorly understood.Using a controlled cortical impact (CCI) model of severe TBI in male C57BL/6J mice, we examined the effects of delayed anodal tDCS on hippocampal neurogenesis during chronic recovery. Bromodeoxyuridine (BrdU) was administered one-month post-injury to label proliferating cells, followed by ten daily 20-minute sessions of 250 µA anodal tDCS. CCI significantly reduced $BrdU^+$ cell number in the ipsilateral dentate gyrus, and this proliferative deficit was reversed by tDCS. To assess neuronal lineage, we quantified the co-labeled BrdU+/DCX+ population - cells born during the labeling window that had committed to a neuronal fate. tDCS significantly increased this co-labeled population in the ipsilateral dentate gyrus, demonstrating that a subset of tDCS-responsive proliferating cells differentiate toward a neuronal identity. This population represented ~10% of the total BrdU+ pool, suggesting that the effects of tDCS may extend beyond immature neurons and involve broader impacts on cell survival and non-neuronal cell fates. Sholl analysis revealed no increase in dendritic complexity or morphological maturation of DCX+ cells. These findings suggest that tDCS supports early neuronal differentiation but does not enhance structural maturation during this time window in TBI. However, tDCS may still exert effects on established neuronal circuits and synapses. These findings indicate that tDCS partially restores the neurogenic response to TBI by rescuing proliferation and promoting neuronal fate adoption in a subset of newly born cells. The effects of tDCS on cell survival and mature synapses as well as non-neuronal cells is an avenue for future investigation. An important limitation of the current study is that the 10-day stimulation protocol does not span the full 4–6-week window over which newborn dentate granule cells undergo dendritic arborization and synaptic integration. It is therefore possible that tDCS was not sustained long enough to drive morphological maturation to completion. Future studies will examine stimulation protocols spanning this critical maturation window, alongside labeling for $BrdU^+/NeuN^+$ to assess whether newborn neurons achieve mature neuronal identity.

Disclosures: S.G. Haney: None. **D. Gondalia:** None. **J.Y. Su:** None. **B.S. Main:** None. **J.D. O'Leary:** None. **M.P. Burns:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.08/D19

Topic: A.01. Neurogenesis and Gliogenesis

Support: AA028200

Title: Ethanol Exposure via Lactation Alters Hippocampal Neurogenesis During Postnatal Development in Mice

Authors: I. ISKUSNYKH[1], S. THAPA[2], V. V. CHIZHIKOV[1], *A. BUKIYA[2];
[1]Anat. and Neurobio., UTHSC, Memphis, TN; [2]The Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Ethanol exposure during early brain development is associated with long-term cognitive and neurological impairments; however, the mechanisms by which maternal alcohol consumption affects hippocampal maturation in offspring remain poorly understood. In this study, we used a mouse model of postnatal ethanol exposure using pregnant C57BL/6J mice to mimic maternal ethanol consumption during the lactation period and ethanol transmission through breast milk. Ethanol (6 g/kg) was administered to lactating dams every 12 hours from postnatal day 0 (P0) to postnatal day 10 (P10) via oral gavage. This protocol allowed ethanol exposure of pups during a critical period of brain development (3rd trimester-equivalent of human pregnancy). The control group of lactating dams was receiving gavages of distilled water.Blood ethanol concentrations measured in dams 2 hours after the first gavage and in pups 12 hours after the final maternal gavage averaged 130 and 67 mg/dL, respectively. Brains were harvested from male and female P10 pups. Using immunohistochemistry (IHC), we investigated the impact of ethanol exposure on neurogenesis within the dentate gyrus of the hippocampus. Ethanol exposure via lactation significantly reduced the numbers of both phospho-histone H3-positive (pH3+) proliferating progenitor cells and Calbindin-positive cells. These findings suggest that maternal ethanol consumption during lactation impairs progeny brain neurogenesis by disrupting progenitor cell proliferation and may consequently compromise neuronal maturation during hippocampal development.Thus, our findings demonstrate that maternal ethanol consumption during lactation adversely affects hippocampal development by impairing neuronal proliferation and maturation. Our findings may facilitate the identification of new therapeutic strategies for neurodevelopmental disorders associated with alcohol exposure.

Disclosures: I. Iskusnykh: None. **S. Thapa:** None. **V.V. Chizhikov:** None. **A. Bukiya:** None.

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.09/D20

Topic: A.01. Neurogenesis and Gliogenesis

Title: Effects of pre- and early postnatal lead ion toxicity on the motor cortex and locomotor activity in rats.

Authors: *M. MIKADZE[1,2], T. BIKASHVILI[1];
[1]Neurotoxicology, Ivane Beritashvili Ctr. of Exptl. Biomedicine, Tbilisi, Georgia; [2]Ilia State Univ., Tbilisi, Georgia

Abstract: Exposure to lead during the early stages of pregnancy and the prenatal period is quite risky and may result in serious health issues later on. When assessing the neurodevelopmental toxicity of lead exposure, most epidemiological studies have taken gender into account as a confounding factor. The impact of prenatal lead ions on locomotor activity in connection to motor cortex architecture is discussed in this research. The findings for both male and female rats are discussed. Experiments were conducted on the offspring of Wistar rats that were given lead acetate at a) 0%, b) 0.05%, and c) 0.2% with water throughout pregnancy and lactation. Atomic absorption spectrophotometry was used to determine the lead content of blood.The overall degree of locomotor activity was evaluated using Calvin S. Hall's Open Field Test. Histological analysis of the density of motor cortex neurons was conducted using a light microscope.The number of neurons in the motor cortex of the experimental pups' brains decreased statistically significantly during the important days of neurogenesis, PD7, PD14, PD21, and PD28, as compared to the results of the pups in the control group. PD61 progeny or young adult rats were used in the second set of experiments.In the open field test, male rats showed a statistically significant decrease in locomotor activity, as measured by the number of lines traversed, which was not observed in female rats.Morphological analysis showed that at both low and high dosages, there was a tendency for both sexes' offspring to have fewer motor cortex neurones; however, in male rats at the high dose, this decline was statistically significant. Our findings demonstrate that lead exposure during pregnancy lowers the motor cortex's neuronal density. Later on, this manifests as motor activity. However, because it was statistically significant in male offspring, this violation is gender-dependent. We can hypothesise that compared to female rats, the growing male rats' motor region of the brain is significantly more vulnerable to lead ion exposure.

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

Poster

PSTR252: Postnatal Neurogenesis: Molecular, Circuit, and Pathological Determinants of Neural Stem Cell Fate

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR252.10/D21

Topic: A.01. Neurogenesis and Gliogenesis

Support: RM1MH138309

Title: Brain-wide, pan-cellular map of postnatal mouse brain development

Authors: *E. HAN, I. E. BJERKE, J. PI, L. STAEBELL, Y. KIM;
Dept. of Neurosci. and Exptl. Therapeut., Penn State Univ., Hershey, PA

Abstract: Developing brains undergo regionally distinct volume expansion with birth of new cells, their migration, and programmed cell death across different developmental stages. Altered brain volume with cellular changes has been frequently implicated in many neurodevelopmental disorders. Despite its significance, the overall changes in total cell count and density in developing brains remains poorly understood. To address this issue, we quantified cell numbers and densities across the whole brain in the developing mouse. Mouse brains from postnatal days (P) 4, 6, 8, 10, 12, 14, 28, and 56 were collected and underwent tissue clearing with Sytox Deep Red Nucleic Acid followed by using light-sheet fluorescence microscopy (LSFM) imaging. We used a deep-learning model (Cellpose) to detect labeled cells and age-matched reference brains were used for brain-wide quantification. Cell number reaches steady state at P14 for most brain areas, except in the hindbrain, where cell number continues to increase until P28. Brain volume continuously increases until P56, although the rate of growth slows down at P14. The increase in volume was high relative to that of total cell counts, resulting in a consistent decrease in cell density across all brain regions. In summary, our data provides the first pan-cellular, brain-wide quantification of postnatally developing mice, providing foundational insights into the dynamics of brain development.

Disclosures: E. Han: None. **I.E. Bjerke:** None. **J. Pi:** None. **L. Staebell:** None. **Y. Kim:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.01/D22

Topic: A.06. Developmental Disorders

Support: NSF PRIME program Texas Woman's University (to MH)
Robert A. Welch Foundation (to MH)
Daisy Brand Research Grant (to MH)
Jane Nelson Institute for Women’s Leadership (to ES)
Quality Enhancement Plan (QEP) (to ES)
TWU Division of Biology
Project ACCESS

Title: mTORC2 Hyperactivation is Associated with Alterations in Neurexin-1/Rab Colocalization: A Potential Mechanism for Presynaptic Dysfunction in Autism

Authors: *M. HUTTON[1], E. SWENSEN[3], D. L. HYNDS[2];
[1]Chem. and Biochem., [2]Biol., Texas Woman's Univ., Denton, TX; [3]Biol., Texas Womans Univ., Denton, TX

Abstract: Autism Spectrum Disorder (ASD) is characterized by altered synaptic connectivity associated with the disruption of Neurexin-1 (NRX1), a presynaptic adhesion protein essential for synapse formation. Prior work in our lab suggests that NRX1 transport to presynaptic terminals is mediated by specific Rab GTPases Rab3A, 27A, and 37, as well as the anterograde kinesin protein KIF1A. Simultaneously, hyperactivation of the mammalian target of rapamycin (mTOR) signaling pathway is a known mechanism underlying ASD pathology. mTORC2 mediates the cytoskeletal organization required for vesicle transport. We hypothesize that mTORC2 hyperactivation disrupts the actin-microtubule architecture required for Rab-mediated NRX1 delivery to the presynaptic terminal. To test this, we established an in vitro model utilizing B35 rat neuroblastoma cells cultured in serum-complete media (SCM) to maintain proliferation, or serum-free media (SFM) to induce neuronal differentiation. mTORC2 hyperactivation was induced via insulin treatment. Fluorescent immunocytochemistry (ICC) and confocal microscopy were utilized to label NRX1, transport markers, and mTORC2 constituents. Quantitative colocalization and morphological changes were analyzed using ImageJ/FIJI. In differentiated B35 cells, NRX1 was colocalized with Rab GTPases, specifically Rab3A, KIF1A, and mTORC2 constituents RICTOR and AKT, confirming the presence of an active vesicular transport complex associated with mTOR signaling networks. Furthermore, insulin-treated B35 cells successfully modeled the aberrant morphological phenotypes characteristic of neurodevelopmental disorders, revealing statistically significant structural alterations, including a notable increase in soma area ($p = 0.0026$) and altered dendrite complexity ($p = 0.0226$) compared to untreated controls. These results suggest that excessive mTORC2 activity may destabilize the structural tracks necessary for accurate NRX1 delivery, providing a mechanistic link between abnormal mTOR signaling and presynaptic dysfunction in ASD. These findings offer potential biomarkers for tracking pre- and post-intervention.

Disclosures: M. Hutton: None. **E. Swensen:** None. **D.L. Hynds:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.02/E1

Topic: A.06. Developmental Disorders

Support: 1K08NS112598-01A1

Title: Inhibition of DNA methylation reduces spontaneous hyperactivity in TSC2-deficient neurons

Authors: *S. DEROSA[1], K. D. WINDEN[2], W. AFSHAR SABER[2], M. SAHIN[2];
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Abstract: Neurodevelopmental disorders (NDDs) encompass a wide range of neurological disorders, from epilepsy to behavioral and cognitive symptoms. Progress has been made in understanding the underlying genetics, however, these advances have not yet translated into effective therapeutics. Tuberous Sclerosis Complex (TSC) is a genetic disorder associated with high rates of NDDs and is caused by variants in either *TSC1* or *TSC2*. These genes are important regulators of the mechanistic target of rapamycin (mTOR). mTOR therapies have been investigated for neurological symptoms with limited success, suggesting the involvement of alternative mechanisms beyond mTOR in TSC. We observed that the mTOR inhibitor, rapamycin, was effective in rescuing hyperactivity and gene expression during early neuronal differentiation. However, rapamycin treatment after neuronal differentiation was not only ineffective in correcting activity, but also had limited effects on gene expression. Interestingly, persistently dysregulated genes were associated with alterations in DNA methylation, leading to the hypothesis that modifying DNA methylation might rescue neuronal abnormalities in TSC. We utilized an isogenic series of induced pluripotent stem cells (iPSCs) with all TSC2 genotypes. iPSCs were differentiated into neurons using a patterning step and induction of the transcription factor Neurogenin-2. We treated neurons with 5-Aza-2'-deoxycytidine, a DNA methylation inhibitor that leads to global hypomethylation, alone at day 10 of differentiation or in combination with rapamycin at day 30. We recorded spontaneous neuronal activity using multielectrode arrays (MEAs). We observed that 5-Aza-2'-deoxycytidine alone was capable of reducing spontaneous activity and that treatment with both this compound and rapamycin decreased spontaneous activity at later timepoints. These data show that modification of genomic methylation can directly influence the activity of TSC2-null neurons and reestablish the efficacy of mTOR inhibition later in differentiation. Ultimately, these data highlight the therapeutic potential of DNA methylation interventions in treating the neurological symptoms of TSC patients.

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Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.03/E2

Topic: A.06. Developmental Disorders

Support: NIH Grant MH132921

Title: Autism-associated loss of δ-catenin functions alters prefrontal activity and disrupts social behavior

Authors: V. MAI, H. KIM, S. ROH, V. CORREA, ***S. KIM**;
Colorado State Univ., Fort Collins, CO

Abstract: Research suggests that synaptic activity and signaling can regulate social behavior. However, the links between synaptic regulation and social behavior are not completely understood. δ-catenin functions as an anchor for the glutamatergic AMPA receptor (AMPARs) to regulate synaptic activity in excitatory synapses. Mutations in the *δ-catenin* gene are found in autism patients from multiple families and induce a loss of δ-catenin functions at excitatory synapses, which is thought to be the etiology of autism in people. Recent studies suggest that the loss of δ-catenin functions significantly decreases cortical neurons' inhibition to increase excitation. Postsynaptic glutamatergic activity in excitatory and inhibitory cells in the medial prefrontal cortex (mPFC) regulates cellular excitation and inhibition, which is essential in the control of social behavior in humans and animals. Research also suggests that parvalbumin-positive (PV+) inhibitory interneurons in the mPFC receive direct glutamatergic inputs from multiple brain areas to drive feedforward inhibition onto prefrontal pyramidal neurons, which is important for the regulation of social behavior. Here, we demonstrate that glutamatergic activity is significantly reduced in knockout (KO) PV+ cells in the layer 2/3 mPFC. Consistently, inhibitory activity is decreased in KO prefrontal pyramidal cells. Additionally, we develop a new social behavior test using round social arena to evaluate freely moving animals' behaviors and reveal that social behavior is disrupted in δ-catenin KO mice.Therefore, δ-catenin is important for glutamatergic activity in PV+ inhibitory interneurons to provide feedforward inhibition onto pyramidal neurons in the mPFC, which regulates social behavior. This suggests disrupted feedforward inhibition and excitation and inhibition imbalance, which is likely responsible for social impairment in KO mice.

Disclosures: V. Mai: None. **H. Kim:** None. **S. Roh:** None. **V. Correa:** None. **S. Kim:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

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Topic: A.06. Developmental Disorders

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NIH HD097327 (MBB)
NIH EY027881 (PAR)
NIH P30 HD018655

Title: Selenoprotein gene expression is downregulated in plasma exosomes from human preterm infants

Authors: *C. M. ELITT[1,3], G. KRIKORIAN[2], E. KIM[2], A. CHENG[2], E. CHOE[4], J. WANG[2], M. ROSS[2], J. M. DREYFUSS[5], T. E. INDER[6], L. BALAJ[7], H. CHRISTOU[8], Z. HE[1], M. B. BELFORT[8], P. A. ROSENBERG[3];
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Abstract: We have found reduced whole blood selenium concentration in very preterm infants (VPT) is associated with smaller brain and body growth at term. Exosomes are microvesicles secreted by all cells and are detectible in body fluids including blood. Exosomal RNA transcripts of selenoprotein genes may provide a window into brain development and injury in preterm infants. We hypothesized differences in gene expression in selenoproteins detectible in plasma exosomal RNA in (VPT) at term compared with full-term infants (FT). We collected at discharge 0.5-1 mL of blood from 33 VPT [gestational age at birth (GA) 24-30 weeks; at discharge 40.7±3.3 weeks], and cord blood from 15 healthy FT [(GA) 37-39 weeks]. Exosomal RNA was harvested and RNAseq performed. Differential expression analysis for all 25 selenoproteins was performed comparing VPT with FT. Significance was assessed using adjusted p-values. There were significantly decreased expression of selenoprotein and selenocysteine machinery transcripts in the VPTs at term compared to FT infants: low-density lipoprotein receptor-related protein 8 [(LRP8; the receptor for selenoprotein P) decreased 1.96 fold; $p_{adj} = 0.0284$], selenoprotein W [(SELENOW) decreased 1.75 fold; $p_{adj} = 0.0336$], selenoprotein V [(SELENOV) [decreased 5.86 fold; $p_{adj} = 0.0434$], methionine sulfoxide reductase B1 [(MSRB1) decreased 2.00 fold; $p_{adj} = 0.0171$], iodothyronine deiodinase 1 [(DIO1) decreased 4.06 fold; $p_{adj} = 0.0245$]. In contrast, selenoprotein F (SELENOF) had increased expression in VPTs at term compared to FT infants (increased 1.82 fold; $p_{adj} = 0.0152$). Selenoprotein RNA transcripts are detectible in plasma exosomes and most are downregulated in VPT compared to FT infants, implicating thyroid hormone synthesis (DIO1), oxidative stress (SELENOW, SELENOV, MSRB1) and selenium transport (LRP8). LRP8 is of particular interest as the receptor for the major selenium carrier in the blood (selenoprotein P) and is highly expressed at the blood-brain barrier.

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Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.05/E4

Topic: A.06. Developmental Disorders

Support: Shota Rustaveli National Science Foundation of Georgia # FR-21-4759

Title: Propionic acid affects mitochondrial number and mitochondria-derived vesicles: electron microscopic study

Authors: *M. G. ZHVANIA, -;
Ilia State University, Ivane Beritashvili center of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: The goal of the study was the evaluation of the effects of propionic acid on mitochondrial ultrastructure and mitochondria-derived vesicles in relevance to autism spectrum disorder pathology. Transmission electron microscopy was used to measure mitochondria associated with single- and double-membrane vesicular structures within neuronal compartments of the medial prefrontal cortex. Specifically, the analysis focused on mitochondrial profiles located in the perikarya, dendritic processes, and synaptic regions of adolescent male Wistar rats. Tissue samples were collected 10 days following a single intraperitoneal administration of middle dose of propionic acid (175 mg/kg) allowing for ultrastructural assessment of mitochondrial alterations in relation to vesicle formation within these subcellular domains. Electron-microscopy quantitative analysis shows that the number of mitochondria with single-membrane vesicles are significantly higher than the mitochondria with the double-membrane in all evaluated compartments of control and propionic acid-treated animals. Propionic acid significantly reduced the number of mitochondria with single-membrane vesicles in all areas except in the neuronal processes. In contrast, the number of mitochondria with the double-membrane vesicles were significantly increased in the presynaptic area following propionic acid treatment. The data indicate that propionic acid differentially affects the number of mitochondria with the single- vs double- membrane vesicles in the medial prefrontal cortex. Since propionic acid is used to mimic autism spectrum disorder, the noted differences between its effects on these mitochondrial structures may suggest using them as one of the potential markers in this state.

Disclosures: M.G. Zhvania: None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.06/E5

Topic: A.06. Developmental Disorders

Support: 1ZIAMH002881

Title: The Neurodevelopmental Disorder-linked Protein AIDA-1 Supports PV Neuron Firing and Gamma Oscillations by Promoting Mitochondrial Fusion

Authors: *D. PANJA[1], R. TIAN[2], X. MA[2], H. COATL-CUAYA[3], Y. LI[4], Z. LI[5];
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Abstract: The brain is among the most metabolically active organs, relying on mitochondria as the primary energy source. Neuronal energy expenditure is dominated by synaptic transmission and is proportional to spiking rates, which vary across neuron types. Fast-spiking activity imposes exceptional energetic demands in neurons such as Parvalbumin-expressing (PV) interneurons, which generate gamma oscillations that are frequently impaired in neurodevelopmental disorders (NDDs). However, most studies of neuronal mitochondria have focused on excitatory neurons with relatively low spiking rates; how fast-spiking neurons meet their energetic demands, and whether their metabolic constraints contribute to NDD pathophysiology, remain unclear. To address this, we applied 40-Hz audiovisual stimulation in mice to induce gamma oscillations and performed PV neuron-specific mitochondrial proteomics. Mitochondrial ATP levels and translocation of cytosolic proteins to mitochondria were assessed using super-resolution imaging, and mitochondrial fusion was measured using photoactivatable, mitochondria-targeted GFP. Gamma oscillations were recorded *in vivo*, and PV neuron electrophysiological properties were analyzed in acute brain slices. We found that AIDA-1 (amyloid-β protein precursor intracellular domain-associated protein-1) accumulated on PV neuron mitochondria following 40-Hz stimulation. Haploinsufficiency of AIDA-1 causes Anks1b haploinsufficiency syndrome (ANDS), a neurodevelopmental disorder. AIDA-1 in PV neurons interacts with mitofusin 2 (Mfn2) to promote mitochondrial fusion and ATP production during gamma activity. Conversely, heterozygous loss of AIDA-1, reflecting human NDD mutations, reduces PV neuron spiking and gamma oscillations. These findings indicate that PV neurons increase energy supply through AIDA-1-regulated mitochondrial fusion and implicate disrupted mitochondrial dynamics and energy metabolism in the neural network dysfunction associated with NDDs.

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Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Program #/Poster #: PSTR253.07/E6

Topic: A.06. Developmental Disorders

Support: NIH Grant 1R35GM146782
Autism Spectrum Program of Excellence

Title: Temporal shifts in neurexin and neuroligin function reveal plasticity in a social feeding circuit

Authors: *F. M. HOLLOMAN[1], M. P. HART[2];
[1]Univ. of Pennsylvannia, Philadelphia, PA; [2]Univ. Pennsylvania, Philadelphia, PA

Abstract: Cell Adhesion Molecules (CAMs) regulate how neurons connect and communicate to form circuits that are crucial for brain function and behavior. CAM genes have been associated with pathological mechanisms of neurological and neurodevelopmental disorders (NDDs). Some disorders associated with CAM genes show age-specific behavioral phenotypes that change across the lifespan, but the molecular and circuit mechanisms by which they can impact behavior across the lifespan is poorly understood. Understanding how these genes and their disruption influence circuit structure and function across development is essential, especially whether resulting behavioral changes are permanent or reversible. Many disease-relevant CAM genes are conserved in *Caenorhabditis elegans* (a small nematode), offering an ideal model to study these genes across the lifespan at multiple levels. We found that loss of neurexin (*nrx-1*) or neuroligin (*nlg-1*) reduces social feeding behavior of day 1 adults. In the wild, *C. elegans* feeding behavior ranges from solitary where animals avoid contact, to highly social where they aggregate in large groups. To investigate when these CAMs are critical for this behavior, I used the auxin-inducible degron system to temporally and spatially control the endogenous protein expression of NRX-1 and NLG-1. Degrading the CAMs during development or at the beginning of larval stage (L4), reduced social feeding behavior of day 1 adults highlighting its importance during development and late development. Interestingly, degrading NRX-1 only during day 1 of adulthood reduced social feeding, showing its functional importance after development. But NLG-1 degradation at day 1 did not impact behavior, demonstrating only a development role. Further, I compared *nrx-1* and *nlg-1* function in Day 1 and Day 4 adults in social feeding behavior. I found that loss of *nrx-1* reduces behavior during early adulthood but not mid-adulthood (day 4). In contrast, loss of *nlg-1* decreases social feeding in day 1 and day 4 adults. These results indicate that *nrx-1* is required for social feeding in development and early adulthood, but becomes dispensable, while *nlg-1* is required for development of social feeding circuit that has a stable impact on behavior throughout all of adulthood. To understand the mechanisms by which CAMs temporally alter the circuit that regulates these behavioral changes, I am comparing pre-synaptic puncta of known sensory neurons to the RMG interneuron (which integrates and drives social feeding behavior), measuring activity of the RMG neuron across adulthood via calcium imaging and investigating how changing avoidance circuit impacts social feeding behavior.

Disclosures: F.M. Holloman: None. **M.P. Hart:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Topic: A.06. Developmental Disorders

Support: UNAM-PAPIIT IN216023
UNAM-PAPIIT IN218924
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Title: Early postnatal thalamic circuit dysfunction drives tactile hyposensitivity in Shank3B mutant mice

Authors: *R. A. MEJIA-ORTIZ[1], M. G. MARTÍNEZ-MONTALVO[2], P. GONZALEZ-PEREYRA[2], M. PALOMERO RIVERO[1], P. E. RUEDA-OROZCO[2], V. G. LOPEZ HUERTA[1]; [1]Neurodevelopment and Physiol., Inst. de Fisiología Celular, Univ. Nacional Autónoma de México, Ciudad de Mexico, Mexico; [2]Neurobio. of Develop. and Neurophysiol., Inst. de Neurobiología, Univ. Nacional Autónoma de México, Querétaro, Mexico

Abstract: Proper neurodevelopment depends on sensory experience, which refines sensory, motor, and cognitive functions via intricate thalamocortical (TC) and corticothalamic loops. Early tactile processing plays a key role in shaping social behavior and communication, domains that are severely affected in autism spectrum disorders (ASD). However, the early mechanisms underlying tactile dysfunction in ASD remain poorly understood.
In this work, we investigated tactile processing in Shank3B KO mice, a well-established ASD model. At early stages, Shank3B KO mice presented tactile hyposensitivity during hind-paw stimulation, a phenotype that evolved into hyperreactivity in adulthood. To identify the neural substrates underlying tactile deficits, we performed ex vivo patch clamp recordings along the somatosensory pathway in juvenile mice. The ventrobasal (VB) thalamus showed the most robust alterations: increased rheobase, reduced firing rate indicating intrinsic hypoexcitability, and a balanced reduction of both excitatory and inhibitory postsynaptic currents. In vivo electrophysiological recording further demonstrated hypoactivity during tactile stimulation, accompanied by an increased number of responsive neurons, suggesting a compromised sensory encoding and a reduced signal-to-noise ratio (SNR). Optogenetic activation of VB neurons failed to rescue the deficit, confirming that disrupted encoding, rather than simple hypoactivity, underlies the tactile phenotype. Notably, chemogenetic enhancement of the thalamic reticular nucleus mediated lateral inhibition significantly improved sensitivity, most likely by reducing noise, restoring SNR, and refining sensory encoding.
Altogether, these results establish early postnatal TC circuit dysfunctions as a core driver of tactile hyposensitivity in Shank3B mice and suggest that targeting these circuits may offer new therapeutic approaches for sensory and cognitive deficits in ASD.

Disclosures: R.A. Mejia-Ortiz: None. **M.G. Martínez-Montalvo:** None. **P. Gonzalez-Pereyra:** None. **M. Palomero Rivero:** None. **P.E. Rueda-Orozco:** None. **V.G. Lopez Huerta:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.09/E8

Topic: A.06. Developmental Disorders

Support: TWU Division of Biology
TWU Research Enhancement Program
Department of Education Project ACCESS

Title: Kinesin motor regulation of neurexin-1 and rab3 synaptic localization in Caenorhabditis elegans

Authors: *E. SWENSEN, T. GUMIENNY, D. L. HYNDS;
Texas Womans Univ., Denton, TX

Abstract: Long-range anterograde axonal transport driven by kinesin molecular motors is essential for presynaptic cargo delivery, vesicle release, and precise maintenance of neural circuit development. Pathogenic mutations in motors like KIF1A and KIF5 disrupt axonal transport machinery, driving severe neurodevelopmental delay, spastic paraplegia, and intellectual disability. This study defines how specific kinesin motors and their adaptors regulate the synaptic localization of the presynaptic cell-adhesion molecule neurexin-1 (NRX-1) and its critical vesicle regulator, the small GTPase RAB-3, within *Caenorhabditis elegans*. NRX-1 plays a critical role in organizing trans-synaptic signaling and structural alignment, while RAB-3 is essential for synaptic vesicle docking, priming, and fusion at active zones. We are evaluating transgenic *C. elegans* strains expressing *nrx-1::GFP* (strain PHX3578) and *mCherry::rab-3* (strain IZ975) crossed with deletion mutants for *unc-104* (KIF1A), *unc-116* (KIF5), *unc-16* (JIP3 cargo adaptor), and the meiotic kinesin isoform *klp-15* as an external transport control. GFP and mCherry reporter strains were acquired from Dr. Michael Francis at the University of Massachusetts. A double-mutant reporter strain expressing *nrx-1::GFP; mCherry::rab-3* has been confirmed via fluorescent expression; mutants for *unc-104*, *unc-116*, *unc-16*, and *klp-15* were obtained from the Caenorhabditis Genetics Center (strains RB992, FF41, CB109, and RB1593). After successful generation and genotyping of triple mutants (double reporter crossed with kinesin mutant(s) of interest), high-resolution confocal imaging of green and red puncta in dorsal and ventral nerve cords is performed. Quantitative analysis of both fluorescence intensity and puncta density at active zones is used to identify indispensable motor isoforms and track cargo-specific transport deficits. We hypothesize that *unc-104/116/16* mutants will exhibit a dramatic loss or mislocalization of *nrx-1::GFP* and *mCherry::rab-3* fluorescence at synaptic active zones. Conversely, mutations in *klp-15* are expected to cause little to moderate reduction, suggesting a specialized or redundant role in NRX-1 trafficking to synapses. These findings aim to advance our fundamental understanding of molecular motor coordination in vivo, clarifying the foundational mechanisms of human synaptopathies.

Disclosures: E. Swensen: None. **T. Gumienny:** None. **D.L. Hynds:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Pew Trust repatriation fund (FJB)

Title: Epigenetic dysregulation of Kcc2 during neurodevelopment in monogenic models of autism spectrum disorder

Authors: *F. GALLEGUILLOS[1,2,3], E. AMADEI[2,3], M. PEDRAZA[2], E. QUIÑONES-MEDINA[2], C. AHUMADA[2,3], F. J. BUSTOS[2,3];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impairments in social interaction, communication and repetitive behaviors, often accompanied by cognitive deficits and anxiety. Although ASD exhibits high heterogeneity, syndromic forms converge on disruptions of the excitatory/inhibitory (E/I) balance during brain maturation. The K+/Cl- cotransporter 2 (KCC2) plays a key role in this process, which drives the developmental shift from excitatory to inhibitory GABAergic signaling by lowering intraneuronal chloride concentration. Reduced KCC2 expression has been consistently reported in ASD patients and animal models and linked to disruptions in the E/I balance, contributing to altered neuronal maturation and circuit function. Here, we report two unrelated monogenic ASD models generated using CRISPR/Cas9 that show reduced KCC2 expression. 1. VPS50-KO mice that display impaired learning and memory, reduced sociability, and increased anxiety and 2. MeCP2-KO related to Rett Syndrome. We propose that KCC2 downregulation is driven by epigenetic changes at its promoter. Using mouse primary cortical neurons transduced with AAV-CRISPR/Cas9 to produce VPS50-KO or MeCP2-KO we evaluated epigenetic mechanisms regulating *Kcc2* expression at the promoter through bisulfite-sequencing analysis of DNA methylation and Chromatin immunoprecipitation analysis of histone modifications.In addition, we evaluated neurons at 3 Days in vitro (DIV) as an immature control, characterized by low *Kcc2* expression and an excitatory response to GABA, whereas 15 DIV neurons served as mature controls with high *Kcc2* expression. 3DIV neurons showed higher DNA methylation and lower histone tail acetylation levels (H3K9Ac and H3K27Ac) at the Kcc2 DNA promoter region compared with mature neurons (15 DIV), consistent with the developmental increase in *Kcc2* expression. In contrast, both ASD models exhibited increased DNA methylationand reduced enrichment of activating histone acetylation marks (H3K9Ac and H3K27Ac) at the Kcc2 promoter, suggesting both models arrest Kcc2 in a repressed, immature epigenetic configuration during maturation. Our findings identify Kcc2 epigenetic dysregulation as a convergent molecular mechanism across genetically distinct ASD models. Future experiments will try to use epigenetic editing tools to restore KCC2 expression in ASD as a potentially therapeutic approach.

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Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Program #/Poster #: PSTR253.11/F2

Topic: A.06. Developmental Disorders

Support: NIH Grant: 1R56MH130599-01A1

Title: Altered Distribution of Perineuronal Nets in the Arid1b Haploinsufficient Brain Across Development and Regions

Authors: *J. ACKERMAN[1,2], S. KATTEWAR[1], T. FORD[1], W.-Y. KIM[1];
[1]Dept. of Biol. Sci., [2]Dept. of Biomed. Sci., Kent State Univ., Kent, OH

Abstract: Haploinsufficiency of the *AT-Rich Interactive Domain 1B* (*ARID1B*) gene has a causal relationship with autism spectrum disorders (ASD). However, the cellular and molecular mechanisms underlying *ARID1B* haploinsufficiency in the brain remain poorly understood. Our previous study has shown that the genesis, maturation, and function of Parvalbumin (PV) interneurons are impaired in a mouse model of *ARID1B* haploinsufficiency. Perineuronal Nets (PNNs) are an extracellular matrix structure essential for PV neuron maturation and function and are also associated with sex-dependent phenotypes in the brain. Thus, we investigated whether disrupted PNNs are linked to *ARID1B* haploinsufficiency-induced neurodevelopmental abnormalities, with a specific focus on their distribution around PV neurons. Using whole-brain reverse-transcription quantitative polymerase chain reaction, immunohistochemistry, and region-specific stereological quantification, we found alterations in the number of PNNs surrounding PV neurons and in mRNA levels of genes associated with individual components of PNNs in the *Arid1b* haploinsufficient brain across developmental stages and brain regions. *Arid1b* haploinsufficient mice show a potential delay in maturation of PNNs compared to non-mutant mice. Furthermore, the reductions in both the colocalization of PV/PNN and total PNN number were generally less severe in females. This sex-specific difference is particularly noteworthy given the sexual dimorphism observed in ASD, as males are nearly four times more likely to be diagnosed than females. Our data suggests that PNNs may have a crucial role in PV interneuron development and may offer a neuroprotective effect in females, potentially explaining the unequal ratios in ASD diagnoses between sexes.

Disclosures: J. Ackerman: None. **S. Kattewar:** None. **T. Ford:** None. **W. Kim:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Program #/Poster #: PSTR253.12/F3

Topic: A.06. Developmental Disorders

Support: NBRC Core Funds

Title: Proteostasis and Synaptic Dysfunction in Autism Spectrum Disorder

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

Abstract: Autism Spectrum Disorder (ASD) is a genetically heterogeneous neurodevelopmental disorder with concomitant alterations in transcription, disrupting neuronal development. Recent evidence has demonstrated how impaired gene expression affects synaptic function and ASD-associated behaviour. Autistic phenotypes have also been associated with dysregulation of key translation regulators (mTOR, ERK). However, our understanding of the post-transcriptional mechanisms regulating synaptic gene expression remains limited. To this end, we hypothesised that the impairment of protein synthesis and degradation at the synapse due to ASD-linked mutations could affect synaptic proteostasis, thereby affecting synaptic function. To address this, we examine the role of translational and proteasomal proteins in the striatum and cerebellum, regions implicated in numerous ASD phenotypes. Using knock-out rat models of Neuroligin3 (NLGN3) and Neurexin1 (NRXN1), we examine how altered translation and protein degradation affect synaptic activity in adult animals (P70). Specifically, we have analysed the distribution and phosphorylation of translation factors (mTOR, ERK, ribosomal protein S6) and proteasome subunits (Rpt1 and 20S core subunits) at their synaptic compartment. Furthermore, to visualise proteomic changes in striatal and cerebellar synapses, mass spectrometry (MS) will be employed. Using patch-clamp electrophysiology in medium spiny neurons and Purkinje neurons, the effects of differentially expressed proteins on neuronal activity were also analysed. Together, this approach aims to shed light on the role of dysregulated proteostasis in synaptic dysfunction and its contribution to ASD-associated circuit.

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Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

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Topic: A.06. Developmental Disorders

Support: NIH P50HD105351

Title: Human Cortical and Thalamocortical Synaptic Dysconnectivity in ASD

Authors: *J. YOON, B. R. FERGUSON;
Harvard Med. Sch., Boston, MA

Abstract: A major challenge in human neuroscience is understanding the biophysical mechanisms of the dynamic processes underlying neural function. We examined the intrinsic and synaptic properties of human neurons from patients diagnosed with or without autism spectrum disorder (ASD) via patch clamp electrophysiology in acute brain slices, along with post hoc immunohistochemistry (IHC) and functional magnetic resonance imaging (fMRI) data analysis. In ASD, local excitatory cortical synapses had decreased connectivity, with distinct unitary synaptic properties including decreased N-methyl-D-aspartate (NMDA) receptor conductance and shifted short-term synaptic plasticity (STP) exhibiting early facilitation and reduced depression. Conversely, thalamocortical connectivity was increased in ASD, suggesting input-dependent modifications in cortical processing. No differences were found in the intrinsic properties of pyramidal neurons (PNs) or fast-spiking interneurons (FSINs), nor cortical excitation-inhibition (E-I) balance, regardless of association with ASD. These findings represent the first documentation of electrophysiological phenotypes at single-cell resolution obtained from human patients diagnosed with ASD.

Disclosures: J. Yoon: A. Employment/Salary (full or part-time):; Boston Children's Hospital, Harvard Medical School. **B.R. Ferguson:** A. Employment/Salary (full or part-time):; Boston Children's Hospital, Harvard Medical School.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.14/Web Only

Topic: A.06. Developmental Disorders

Title: Chrysin attenuates VPA-induced autistic-like behaviors via HDAC inhibition, BDNF-AKT-mTORC1-SHANK3 restoration, and neuroinflammatory-glial attenuation in rats

Authors: *I. A. ADENIYI;
Physiol., Univ. of Ibadan, Ibadan, Nigeria

Abstract: Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by repetitive behaviors, cognitive and social deficits, and comorbid phenotypes, with rising prevalence. Its unclear pathogenesis and symptom heterogeneity hinder therapy development. Chrysin, a flavone from bee products and plants, shows diverse biological effects but limited ASD studies. Therefore, this study examines chrysin’s impact on ASD behaviors and comorbidities. **Methods:** ASD phenotypes were induced by intraperitoneal VPA (600 mg/kg) administered to pregnant Wistar rats on embryonic day 12.5. Neurodevelopmental milestones were assessed on PND 3-20. Twenty-seven male offspring were allocated into three groups (n=9 each): control, VPA+vehicle, and VPA+chrysin (100 mg/kg p.o., PND 21-42). Behavioural assessments were conducted at PND 21 and 42. Serum corticosterone, pFC and HPC neurotransmitters, cytokines, HDAC, BDNF, and caspase-3 were quantified by ELISA; SHANK3, p-AKT, pS6, IBA-1, and GFAP by immunohistochemistry and Western blot. Data

were analysed by one-way or two-way ANOVA ($\alpha<0.05$). **Results:** VPA-exposed pups exhibited developmental delay relative to controls. Chrysin attenuated hyperalgesia, depressive-like behavior, and anxiety while improving sociability, social novelty, and cognitive function. Serum corticosterone and prefrontal cortex/hippocampal concentrations of serotonin, GABA, and dopamine were elevated; glutamate decreased. Chrysin reduced HDAC and Caspase3 expression while increasing BDNF in both regions. SHANK3, p-AKT, and pS6 were upregulated following Chrysin treatment. Cytokine perturbations were normalized, and IBA-1 and GFAP immunoreactivity were markedly suppressed, reflecting attenuated microglial and astrocytic hyperreactivity. **Conclusion:** Chrysin ameliorated VPA-induced autistic-like behaviours in male Wistar rats through convergent mechanisms: suppression of neuroinflammation and glial hyperreactivity, restoration of E/I neurotransmitter balance, attenuation of apoptotic signalling, normalization of HPA axis activity, and upregulation of epigenetic, mTORC1-translational, and neurotrophic pathways governing synaptic scaffolding protein synthesis.
Keywords: Chrysin, Autism, Shank3, Histone deacetylase, pAKT, pS6

Disclosures: I.A. Adeniyi: A. Employment/Salary (full or part-time):; University of Ibadan.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.15/Web Only

Topic: A.06. Developmental Disorders

Support: 22K07611
25K09819
26K10485

Title: Subcellular and Regional Localization of the Autism-Associated IL-17A Receptors

Authors: *T. SASAKI[1], K. ITAGAKI[2,3], K. NAKAMURA[1,4], Y. KURAMA[1], S. SANAKA[1,4], A. KUBO[1,5], S. KAMIYA[1,5], M. MORIKAWA[6], S. IWATA[1], Y. TAKEI[1];
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Abstract: Accumulating evidence indicates that dysregulation of the immune system contributes to the etiology and pathophysiology of psychiatric disorders. In particular, immune responses mediated by T helper 17 (Th17) cells have been implicated in psychiatric disorders by many clinical studies. However, the processes by which immune responses induce structural changes in the nervous system remain largely unclear, and the contribution of Th17 cells is not yet fully understood. The inflammatory cytokine interleukin-17A (IL-17A) binds to a receptor complex composed of IL-17RA and IL-17RC, thereby inducing inflammatory responses in target

cells.Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in communication and stereotyped behavioral patterns, typically manifesting by 3 years of age. Maternal immune activation (MIA) is considered one of the environmental risk factors for ASD. IL-17A induced in the maternal body by MIA may cross the placenta and act on the fetal brain, contributing to ASD pathogenesis. Although several research groups have reported the distribution of IL-17A and its receptors in the central nervous system, the findings remain inconsistent and controversial. Previous studies in our laboratory showed that mRNAs encoding IL-17A receptors (*Il17ra* and *Il17rc*) are strongly expressed in corticothalamic projection neurons in layer VI of the cerebral cortex.In this study, we used an IL-17RA-specific antibody to analyze the expression pattern of IL-17RA in the mouse brain and its intracellular localization in primary cultured neurons. Immunohistochemical analysis revealed that IL-17RA was observed in the cell bodies and apical dendrites of layer VI neurons. In primary cultured hippocampal neurons at 19-21 days in vitro, IL-17RA was distributed in the cell body and dendrites. These findings are expected to provide insight into the structural and functional changes in the central nervous system induced by inflammatory cytokines, and may contribute to the establishment of a novel pathophysiological model of psychiatric disorders based on neuroimmune interactions, as well as to the exploration of potential therapeutic targets.

Disclosures: T. Sasaki: None. **K. Itagaki:** None. **K. Nakamura:** None. **Y. Kurama:** None. **S. Sanaka:** None. **A. Kubo:** None. **S. Kamiya:** None. **M. Morikawa:** None. **S. Iwata:** None. **Y. Takei:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.16/F5

Topic: A.06. Developmental Disorders

Support: Dana Matthews Neuroscience Research Fund

Title: Alterations in proteins contributing to E/I balance in Shank3B KO mice

Authors: L. FREEMAN[1], M. WILLIAMS[1], S. B. DUTTON[2], ***J. L. LARIMORE**[1];
[2]Biology/ Neurosci. Program, [1]Agnes Scott Col., Decatur, GA

Abstract: SHANK3B is critical for postsynaptic scaffolding at excitatory synapses and is implicated in ASD and SZ. Shank3B knockout mice exhibit ASD-like behaviors and altered E/I balance. Previous work in our lab with Shank3B heterozygote mice demonstrated changes in key protein makers that regulate E/I balance in the hippocampus. Previous work in our lab has also demonstrated that Lion's Mane diet alters the level of vesicular acetylcholine transporter. To study this further, we will analyze protein levels in the hippocampus and pre-frontal cortex of key E/I balance proteins in 8- to 12-week-old wild-type Shank3B+/+ or Shank3B-/- mice in a sex-dependent manner, with and without Lion's Mane. Altogether, these data could reveal sex-

specific E/I protein levels and indicate whether Lion's Mane can alter them, thereby providing potential therapeutic targets for neurodevelopmental disorders.

Disclosures: L. Freeman: None. **M. Williams:** None. **S.B. Dutton:** None. **J.L. Larimore:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.17/F6

Topic: A.06. Developmental Disorders

Support: Dana Matthews Neuroscience Research Fund

Title: Alterations in the gut microbiome in Shank3B KO mice

Authors: *L. FREEMAN[1], M. WILLIAMS[1], S. B. DUTTON[2], J. L. LARIMORE[3]; [2]Biology/ Neurosci. Program, [3]Neurosci., [1]Agnes Scott Col., Decatur, GA

Abstract: The gut-brain axis has been implicated in the pathogenesis and severity of various neurodevelopmental disorders, such as schizophrenia (SZ) and autism spectrum disorders (ASD). SHANK3B is critical for postsynaptic scaffolding at excitatory synapses and is implicated in ASD and SZ. Shank3B knockout mice not only exhibit ASD-like behaviors but also demonstrate altered gastrointestinal epithelium morphology and altered fecal microbiota composition. Previous work in our lab demonstrated increased biodiversity in Shank3B+/- males and reduced biodiversity in Shank3B+/- females compared to wild-type controls. Previous work in our lab has also demonstrated that Lion's Mane reduces anxiety-like and depressive-like behavior. To study this further, we will sequence the gut microbiome from the small intestine of 8- to 12-week-old wild-type Shank3B+/+ or Shank3B-/- mice in a sex-dependent manner, with and without Lion's Mane, and analyze bacterial phyla, classes, orders, families, genera, and species. We will also be comparing behavior in the open field and forced swim tests, as well as key molecular markers in the mice before and after exposure to a Lion's Mane diet. Altogether, these data could reveal sex-specific microbial signatures similar to those we reported in heterozygous mice. This data will also indicate whether Lion's Mane can alter the gut microbiome, thereby providing potential therapeutics targeting the gut microbiota in neurodevelopmental disorders.

Disclosures: L. Freeman: None. **M. Williams:** None. **S.B. Dutton:** None. **J.L. Larimore:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR253.18/F7

Topic: A.06. Developmental Disorders

Support: Tan-Yang Collective
Simons Center for the Social Brain

Title: Socially evoked prefrontal hyperexcitation in Shank3B mutant mice reveals ASD-relevant state-dependent circuit dysfunction

Authors: *X. JIN[1], Z. ZHOU[2], M. ZENG[2], Y. DE ANDA ACOSTA[2], Y. WANG[2], R. FU[2], W. MENEGAS[1], C. ZHANG[1], D. MCCORMACK[1], G. FENG[1];
[1]MIT, Cambridge, MA; [2]Mcgovern Inst. for Brain Res. (MIT), Cambridge, MA

Abstract: Social interaction is essential for adaptive behavior, and altered social communication and interaction are core features of autism spectrum disorder (ASD). SHANK3 encodes a postsynaptic scaffolding protein strongly linked to Phelan-McDermid syndrome and ASD-related social phenotypes. Shank3B mutant mice recapitulate autism-relevant behavioral abnormalities, including impaired social interaction and repetitive grooming, and have been widely used to study how SHANK3 loss alters neural function. Prior studies have identified synaptic, striatal, and prefrontal abnormalities in Shank3 mutant mice, but how neural activity dynamics change across behavioral states, particularly during active social experience, remains less well defined. To address this gap, we examined state-dependent neural activity in male Shank3B mutant and wild-type (WT) mice using functional ultrasound (fUS) and fiber photometry, with fUS providing a large-scale measure of cortical activity and calcium recordings resolving excitatory neuronal activity in orbitofrontal subregions. fUS recordings revealed state-dependent cortical abnormalities in Shank3B mutants, including widespread cortical hypoconnectivity under anesthetized resting-state conditions and large-scale cortical hyperactivation during awake social interaction. To determine whether this social-evoked cortical hyperactivation was associated with increased excitatory neuronal activity in orbitofrontal cortex, we measured calcium responses from CaMKIIα-GCaMP8m-expressing neurons in the lateral orbitofrontal cortex (LOFC) using fiber photometry during freely moving social interaction. Compared with WT controls, Shank3B mutant mice showed elevated social-evoked LOFC calcium responses, indicating increased excitatory neuronal activity in this orbitofrontal region during social experience. In contrast, medial orbitofrontal cortex (mOFC) recordings did not show a comparable genotype-dependent increase, suggesting that social-evoked hyperexcitation is regionally specific rather than uniform across orbitofrontal cortex. Together, these findings indicate that Shank3B loss produces state-dependent cortical dysfunction and identify social-evoked LOFC hyperexcitation as an ASD-relevant physiological phenotype in Shank3B mutant mice. More broadly, altered neural dynamics during active social experience may represent a physiological substrate for altered social processing in SHANK3-related neurodevelopmental disorders.

Disclosures: X. Jin: None. **Z. Zhou:** None. **M. Zeng:** None. **Y. De anda Acosta:** None. **Y. Wang:** None. **R. Fu:** None. **W. Menegas:** None. **C. Zhang:** None. **D. McCormack:** None. **G. Feng:** None.

Poster

PSTR253: Autism: Synaptic and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR253.20/G1

Topic: A.06. Developmental Disorders

Support: Presbyterian Health Foundation (20009147, 20009167) to RP
NIH P20GM103447
P20GM161969-01 (RPL: R.P.)

Title: Primary Cilia Features in GABAergic Interneurons Across Brain Regions and Developmental Stages

Authors: *L. RIGNEY[1], M. IRTZA[3], T. YANG[2], E. TROYANO RODRÍGUEZ[4], R. PATERNO[5];
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Abstract: Primary Cilia Features in GABAergic Interneurons Across Brain Regions and Developmental Stages Lauren Rigney[1], Muhammad Irtza**[2]**, Tingting Yang[1], Eva Troyano-Rodriguez[1], Rosalia Paterno[11]Department of Neurosurgery, University of Oklahoma Health Sciences Center (OUHSC), Oklahoma City, OK 73104[2]Services Institute of Medical Sciences Lahore, Punjab, Pakistan
Primary cilia are sensory organelles that regulate signaling pathways involved in neuronal development, maturation, and circuit formation. Cilia deficits have been reported in various neurodevelopmental disorders, such as autism spectrum disorder or schizophrenia. Although primary cilia have been extensively studied during embryonic brain development, their distribution and properties across GABAergic interneurons throughout postnatal development and adulthood remain poorly understood. We sought to comprehensively characterize primary cilia on GABAergic interneurons across developmental stages and brain regions and to determine whether ciliary features vary across interneuronal subtypes.We characterized primary cilia on GABAergic interneurons across developmental time points and in adulthood in the hippocampus, somatosensory cortex, prefrontal cortex, striatum, and thalamus. GAD2-Cre; Ai14 mice of both sexes were used to label the GABAergic interneuron population. Immunohistochemistry for the ciliary marker adenylyl cyclase 3 (AC3), and FGFR1OP (FOP), a basal body marker, was combined with confocal and super-resolution microscopy to assess cilia prevalence, length, and orientation. Subtype-specific analyses were performed in PV- and SST-expressing interneurons using PV-Cre; Ai14 and SST-Cre; Ai14 mice of both sexes. Primary cilia were present on the majority of GABAergic interneurons across developmental stages and adulthood. In the adult hippocampal CA1 region, approximately 85% of GABAergic interneurons possessed primary cilia with an average length of ~7 μm. Cilia prevalence and morphology varied across developmental stages, brain regions, and hippocampal layers. Within

CA1, cilia were significantly longer in the stratum pyramidale than in other layers, indicating layer-specific regulation. These findings provide a comprehensive characterization of primary cilia across the GABAergic interneuron population throughout development and adulthood. Our results reveal region-, layer-, and subtype-specific differences in cilia features and suggest that primary cilia might play a different role across interneurons subtypes, laying a foundation for subsequent functional studies to better understand the role of cilia during development.

Disclosures: L. Rigney: A. Employment/Salary (full or part-time):; full-time. **M. Irtza:** None. **T. Yang:** A. Employment/Salary (full or part-time):; full-time. **E. Troyano Rodríguez:** A. Employment/Salary (full or part-time):; full-time. **R. Paterno:** A. Employment/Salary (full or part-time):; full-time. 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.; Principal Investigator.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.01/G2

Topic: A.06. Developmental Disorders

Support: NIH Grant R01HD107722
NIH Grant R56HD102898
the Heerman Anesthesia Foundation
the J.H. Modell, M.D., Endowed Professorship

Title: Maternal Stress and Inflammation Mediate Prenatal and Postnatal Transmission of Preconception TBI Effects to Offspring

Authors: Z. KHAN[1], L.-S. JU[1], N. GRAVENSTEIN[1], B. SETLOW[2], ***A. MARTYNYUK**[3]; [1]Anesthesiol., [2]Dept. of Psychiatry, [3]Univ. of Florida, Gainesville, FL

Abstract: Background: Traumatic brain injury (TBI) disproportionately affects young individuals. It can lead to persistent stress, neuroinflammation, and cognitive impairment. There is increased risk of psychiatric illness in the children of TBI affected parents. This study examines intergenerational effects of TBI in young adult females, evaluates maternal pre- and postnatal influences on offspring development, and tests a potential preventive pharmacological strategy. **Methods:** At P60, female Sprague-Dawley rats underwent moderate TBI via midline fluid percussion (F0F_T); a subset received the NKCC1 Cl^- importer inhibitor bumetanide beforehand (F0F_BT), while F0F_T and control (F0F_C) dams received saline. At P90, females were bred with treatment-naïve males to generate F1 offspring. To isolate postnatal effects, from birth to weaning (P21), half of F0F_T offspring were cross-fostered to F0F_C dams and half of F0F_C offspring to F0F_T dams. Behavioral testing began at P130 in F0 females (n=18/group)

and at P50 in F1 offspring (n=18/group/sex), followed by mechanistic analyses, including 16S rRNA gut microbiome profiling in both generations. **Results:** F0F_T females exhibited elevated stress and inflammatory markers and mild alterations in gut microbiome composition, but showed no changes in body weight, behavior, or maternal care. Male offspring of F0F_T dams displayed reduced birth and weaning weights, dysregulated stress and inflammatory signaling, gut dysbiosis, increased anxiety-like behavior, impaired sociability, and deficits in spatial memory. Female offspring of F0F_T dams showed similar reductions in body weight and increased anxiety-like behavior, but were otherwise less affected. Cross-fostering shifted offspring phenotypes toward those observed in the biological offspring of the foster dams reared by their biological mothers. Bumetanide treatment prevented TBI-induced stress, inflammation, and microbiome alterations in F0 females and mitigated most abnormalities observed in offspring. **Conclusion:** These results suggest that, first, TBI induces persistent stress and inflammatory dysregulation in dams, producing sex-dependent neurobehavioral and microbiome abnormalities in offspring via maternal influences on fetal development that may occur from conception to birth, as well as through postnatal mother-offspring interactions. Second, maternal stress and inflammation act as key drivers of these pre- and postnatal effects. Third, NKCC1 represents a potential therapeutic target for mitigating the intergenerational consequences of TBI.

Disclosures: Z. Khan: None. **L. Ju:** None. **N. gravenstein:** None. **B. Setlow:** None. **A. Martynyuk:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.02/G3

Topic: A.06. Developmental Disorders

Support: CHES Zelnick Award
Bigel Endowment Award, Rutgers
C&D Fund
Emch Fund

Title: Cesarean section-associated infant microbiota disrupts mouse hippocampal neurogenesis and microglial colonization

Authors: *X. WANG[1], H. SUN[2], X. ZHOU[3], J. LESSING[3], W. MOHMED[2], E. M. DICICCO-BLOOM[4], M. G. DOMINGUEZ-BELLO[1,2];
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Abstract: The gut microbiome is established during early postnatal life, overlapping with critical periods of brain development, including neurogenesis, apoptosis, and microglial colonization of the hippocampus. Cesarean section (CS), accounting for >30% of births worldwide, disrupts early gut microbial colonization compared to vaginal delivery (VD) and is associated with increased risk of neurodevelopmental disorders (NDDs). Whether CS-associated microbial changes alter hippocampal development remains unclear. To address this question, we collected fecal samples from 1-month-old infants representing two profiles: low-perturbation (VD, no antibiotics, exclusively breastfed, no complications) and high-perturbation (scheduled CS, perinatal antibiotics, formula-supplemented, no complications), with 6 donors per group. Germ-free (GF) Swiss Webster dams received an oral gavage of the human fecal samples at postnatal day 3 (P3), enabling pups to acquire donor-derived microbial communities through maternal contact during nursing and cohousing (hereafter VD and CS mice). Pups were examined at P21. Gut microbial composition was assessed by 16S rRNA gene sequencing. Hippocampal proliferation (EdU), apoptosis (Caspase-3), and microglial density (IBA1) were quantified by immunohistochemistry in both sexes. High-perturbation infant microbiota (CS) resulted in distinct gut microbial profiles in recipient mice at P21 (Bray-Curtis PERMANOVA, $R2=0.14$-0.23, $p\leq0.03$). It also led to reduced alpha diversity (Faith PD, FDR $p<0.05$), without any differentially abundant genera after FDR correction (MaAsLin2, $q>0.05$), suggesting compositional differences reflecting coordinated taxa shifts. In the hippocampus, CS microbiota led to increased proliferation (EdU^+ cells +28%; VD n=9; CS n=11; p=0.009) and reduced apoptosis ($Caspase\text{-}3^+$ cells −33%; VD n=9; CS n=11; p=0.005) compared to mice receiving VD microbiota. Microglial density exhibited a sex-specific effect: CS females had 22% more $IBA1^+$ cells than VD females (VD n=4; CS n=6; p=0.024), whereas males exhibited no differences. In sum, high-perturbation infant microbiota induced overall increased proliferation and reduced apoptosis, with a female-selective elevation in microglia. These changes potentially impact the numbers of cells and synapses. Together, birth mode-associated microbiome differences may alter hippocampal cellular dynamics and neuronal connectivity, providing a mechanistic link between CS-associated microbial disruption and increased NDD risk.

Disclosures: X. Wang: None. **H. Sun:** None. **X. Zhou:** None. **J. Lessing:** None. **W. Mohmed:** None. **E.M. DiCicco-Bloom:** None. **M.G. Dominguez-Bello:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.03/G4

Topic: A.06. Developmental Disorders

Support: NIAAA 5R01AA029114

Title: Ethanol Targets Src Kinase to Trigger Rapid Tyrosine Hyperphosphorylation in DCX+ Immature Neurons

Authors: *J. DOUPE[1,3], M. ANAM[1], B. HOWELL[1], E. C. OLSON[2,3];
[1]Neurosci., [2]Neurosci. and Physiol., Upstate Med. Univ., Syracuse, NY; [3]Developmental Exposure Alcohol Res. Ctr., Binghamton, NY

Abstract: Fetal alcohol spectrum disorder (FASD) is the leading preventable cause of human intellectual disability, yet the underlying biochemical mechanisms responsible for its complex neuropathology remain unclear. Using a pharmacological approach we established that acute ethanol exposure drives rapid protein tyrosine hyperphosphorylation of multiple proteins via Src Family Kinases (SFKs). This response is observed within 15 minutes of ethanol exposure in both the embryonic mouse cortex and human iPSC-derived cortical organoids. As there are eight SFKs, three of which are expressed in the developing cortex and no way to target individual SFKs pharmacologically, it was clear that a genetic dissection was necessary to identify the ethanol responsive kinase. To isolate the specific SFK, we first used *Src*-deficient mouse embryos. Prior immunoprecipitations had suggested that the activation loop of Src, but not Fyn, was phosphorylated in response to ethanol. Consistent with this biochemical result, cortical explants from *Src* knockout embryos revealed a remarkable blunting of ethanol-induced hyperphosphorylation, indicating that Src is the primary SFK responsible for hyperphosphorylation. Further immunohistochemical analysis revealed that this hyperphosphorylation localized predominantly within regions enriched for Doublecortin (DCX+) immature neurons both in mouse explants and human cortical organoids. DCX+ enriched regions represent neurons undergoing migration, neurite outgrowth and Golgi elongation into the apical dendrite, all of which are disrupted following ethanol exposure. Importantly, this tyrosine hyperphosphorylation is not seen in the adult mouse cortex suggesting that immature neurons, specifically those expressing DCX, are uniquely susceptible to ethanol induced Src kinase hyperactivity. Altogether, these findings identify Src kinase hyperactivity in DCX+ immature neurons as a potential trigger for ethanol induced neuropathology associated with FASD.

Disclosures: J. Doupe: None. **M. Anam:** None. **B. Howell:** None. **E.C. Olson:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.04/H1

Topic: A.06. Developmental Disorders

Title: Early edema on T2-weighted and diffusion imaging after neonatal hypoxia-ischemia in mice

Authors: *A. DROBYSHEVSKY;
Endeavor Hlth. Clin. Operations, Evanston, IL

Abstract: Diffusion-weighted (DWI) and T2-weighted MRI have well-described signal evolution in perinatal hypoxic-ischemic brain injury and are often used to diagnose the timing of

the insult and the onset of secondary energy failure in clinical settings. Previous reports indicate differences in the appearance of hyperintensities on T2w images between young and old rats. We revisited the concept using a neonatal mouse hypoxia-ischemia (H-I) model. C57BL/6 mouse pups underwent permanent common carotid ligation followed by 10% oxygen exposure for 60 min at 36 °C at P9. Serial DWI and parametric T2 MRI were performed 30 min, 1,2,6,12,24, 72 hours. Apparent diffusion coefficients (ADC) and T2 maps were calculated. In a subset of animals, the integrity of the blood-brain barrier was assessed using gadolinium contrast. ADC decreased at all time points between 30 min and 24 hours after H-I without normalization, and increased at 72 hours. On the T2-weighted image, hyperintensity was also observed as early as 30 min in some animals, with pronounced enhancement at 1 hour and lasting at least till 72 hours. Parenchymal tissue enhancement on T2-weighted image with gadolinium contrast was observed only starting 4 hours after H-I. Our results indicate that, at least in a subset of pups after neonatal H-I, early T2 changes reflect edema via mechanisms distinct from vasogenic edema yet coincide with cytotoxic edema. Second, there was no bi-phasic change in ADC time course, suggesting a continuum between primary and secondary energy failure without a period of pseudo-normalization. Mechanisms and clinical significance of early edema on T2-weighted MRI remain to be elucidated

Disclosures: A. Drobyshevsky: None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

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Program #/Poster #: PSTR254.05/H2

Topic: A.06. Developmental Disorders

Support: CIRM EDUC4-12759
NIH R01MH094589
NIH R01NS089777

Title: Investigating the pathogenic mechanisms of SATB2 Associated Syndrome through iGONAD generated point mutation mouse models

Authors: *Y. NIE[1], B. CHEN[2];
[1]UC Santa Cruz, Santa Cruz, CA; [2]MCD Biol., Univ. of California Santa Cruz, Santa Cruz, CA

Abstract: SATB2 associated syndrome (SAS) is a severe, autosomal dominant neurodevelopmental disorder characterized by intellectual disability, developmental delay, behavioral challenges, and craniofacial anomalies. SAS is primarily driven by *de novo* mutations in *SATB2*, which encodes a critical chromatin organizer regulating gene expression. While SATB2 is known to dictate callosal versus subcerebral projection neuron identity during cortical development, the distinct pathogenic mechanisms of clinical point mutations remain poorly understood.Leveraging the high efficiency of *in vivo* CRISPR Cas9 genome editing via

iGONAD (improved Genome editing via Oviductal Nucleic Acids Delivery), we selected five clinically severe human SAS mutations (*SATB2* p.R239*, p.E436V, p.R459*, p.G515S, and p.R389C) to construct models in mice. To date, we have established and validated three mutant lines via PCR and sequencing: the point-mutant lines *Satb2*^{436_SAS} and *Satb2*^{515_SAS}, and an intragenic insertion line, *Satb2*^{390_intr}.Mutants across all three validated lines successfully recapitulated clinical SAS phenotypes, including prominent dental anomalies. In the *Satb2*^{436_SAS} line, wild-type (WT), heterozygous (het), and homozygous (homo) mice are fully viable; immunofluorescence (IF) staining of postnatal day 7 (P7) brains is complete and currently undergoing cell quantification. Conversely, homo *Satb2*^{515_SAS} mutants exhibit neonatal lethality within 24 hours of birth, mirroring *Satb2* knockout phenotypes, whereas WT and het survive normally. Western blot analysis revealed that the G515S mutation reduces cortical SATB2 protein levels. Consistently, P0 IF cortical mapping of *Satb2*^{515_SAS} mice demonstrated a marked reduction in superficial layer thickness in both het and homo mutants, accompanied by disorganized deep layer Satb2 expression and an expanded population of Ctip2 positive deep layer neurons. Finally, behavioral profiling of 5-6 month old *Satb2*^{515_SAS} het in open field and Y maze assays revealed significant locomotor hyperactivity, closely modeling behaviors observed in SAS patients.By establishing these novel iGONAD derived mouse models, this study provides powerful tools to dissect variant specific pathogenic mechanisms and accelerate therapeutic discovery for SAS.

Disclosures: Y. Nie: None. **B. Chen:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.06/H3

Topic: A.06. Developmental Disorders

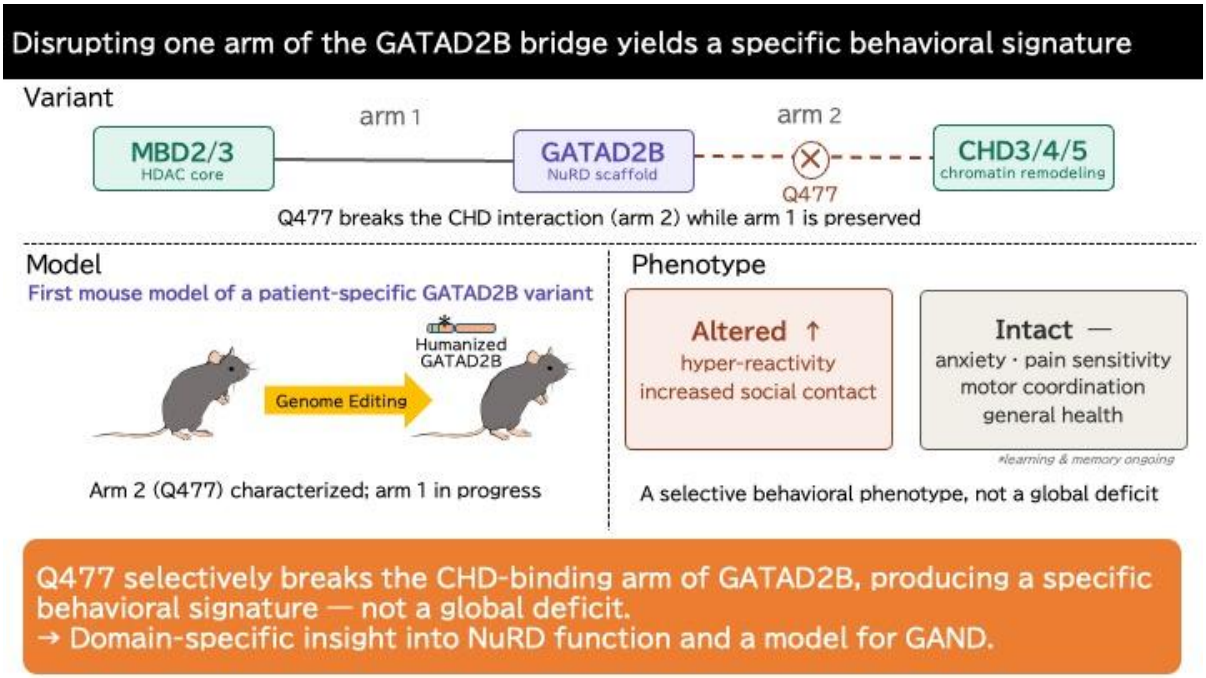
Support: JST CREST (Grant Number JPMJCR23B6)
JSPS KAKENHI (Grant Number 25H00436)

Title: A humanized Gatad2b Q477 knock-in mouse model of GAND exhibits heightened reactivity to novelty and altered social behavior

Authors: *T. WATANABE[1], M. FUKUCHI[2], H. SHOJI[3], T. MIYAKAWA[4], H. NISHIZONO[1]; [1]Kanazawa Med. Univ., Uchinada, Ishikawa, Japan; [2]Fac. of Pharm., Takasaki Univ. of Hlth. and Welfare, Takasaki, Japan; [3]Ctr. for Med. Sci., Fujita Hlth. Univ., Toyoake, Aichi, Japan; [4]Fujita Hlth. University, ICMS, Div. Syst. Med., Toyoake, Japan

Abstract: GATAD2B-associated neurodevelopmental disorder (GAND) is a rare but severe condition marked by intellectual disability, profound language delay, and hypotonia. GATAD2B is a scaffold subunit of the nucleosome remodeling and deacetylase (NuRD) complex, bridging CHD-family remodelers via binding arm 2 and the histone deacetylase core via binding arm 1.

We hypothesized that variants disrupting arm 2 versus arm 1 produce distinct phenotypes. We generated humanized knock-in mice carrying the patient-derived Q477 variant, which disrupts arm 2, by CRISPR-Cas9, and report behavioral data from male heterozygotes (Q477 het, n = 24; wild-type, n = 23). General health screening showed no differences in body weight, body temperature, grip strength, or wire hang latency. In the light/dark transition test, Q477 het mice made more transitions between chambers ($p = 0.022$) and traveled greater distances in the light chamber ($p = 0.020$), with no difference in time spent in the light ($p = 0.167$). In the open field test, het mice showed greater activity during the initial minutes only, while center time was unchanged. The elevated plus maze likewise revealed no differences, together indicating intact anxiety-like behavior and pointing to heightened reactivity to novelty. Hot plate and Rotarod tests showed no differences, indicating intact pain sensitivity and motor coordination. In the social interaction test, Q477 het mice traveled greater distances ($p = 0.003$), made more contacts ($p = 0.006$), and showed greater duration of active contacts ($p = 0.010$). In the three-chamber test, both genotypes showed clear sociability; Q477 het mice also preferred a novel stranger ($p = 0.047$), though heightened reactivity may contribute. These results indicate that heterozygous disruption of arm 2 produces a distinct signature of heightened reactivity to novelty and increased social contact, potentially reflecting the GAND behavioral profile. Memory assessments are ongoing and will be reported, providing further in vivo insight into GATAD2B function within the NuRD complex and a translational platform for GAND.



Disclosures: T. Watanabe: None. **M. Fukuchi:** None. **H. Shoji:** None. **T. Miyakawa:** None. **H. Nishizono:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.07/H4

Topic: A.06. Developmental Disorders

Support: The Health and Medical Research Fund, the Food and Health Bureau, The Government of the Hong Kong Special Administration Region of China (No. 09201116)

Title: Non-invasive Oral Lutein-in-Extra-Virgin-Olive-Oil for Retinopathy of Prematurity: Pre-clinical Assessment and Mechanistic Insights

Authors: *A. C. LO[1], X. YE[2], L. XIANG[2], J.-Y. LEE[3], A. JOUSSEN[4], W. LAM[5]; [1]Dept. of Ophthalmology, The Univ. of Hong Kong, Hong Kong, Hong Kong; [2]Dept. of Ophthalmology, [3]Sch. of Biol. Sci., The Univ. of Hong Kong, Hong Kong, China; [4]Dept. of Ophthalmology, Charité – Universitätsmedizin Berlin, Berlin, Germany; [5]Dept. of Ophthalmology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Retinopathy of prematurity (ROP) is a leading cause of childhood blindness driven by oxidative stress and inflammation, but with limited treatment options. Safe, non-invasive adjunctive strategies become attractive. Lutein is an endogenous xanthophyll carotenoid highly concentrated in the macula and displays antioxidant and anti-inflammatory properties, but its clinical efficacy remains controversial. We proposed that extra-virgin olive oil (EVOO) could enhance lutein absorption, thereby improving its efficacy in ROP. Here, we evaluated the effects of lutein-in-EVOO (LEVOO) in oxygen-induced retinopathy (OIR), a mouse model of ROP. Neonatal C57BL/6J mouse neonates received daily gavage of LEVOO (0.4 μg/g, 1.8 μg/g and 3.6 μg/g of lutein in EVOO) after OIR challenge from postnatal day (P) 12 to P16. Assessments were conducted at P17, including retinal vasculature, function, cytoarchitecture, inflammation, and oxidative damage; serum biochemical and antioxidant profiles; and proteomic analysis and targeted retinal metabolomic analysis. We found that oral supplementation of LEVOO was well-tolerated and safe in mouse neonates without affecting their liver and kidney functions. It reduced retinal avascular and neovascular areas, increased electroretinographic b-wave amplitudes, restored retinal amacrine cells and rod bipolar cells, and protected blood-retinal barrier integrity. LEVOO also alleviated inflammation in the retina via down-regulating activated microglia and elevated interleukin-1β. LEVOO reduced oxidative damage both systemically in the body and locally in the retina. Mechanistically, LEVOO administration inhibited the hypoxia-inducible factor-1α (HIF-1α)-macrophage migration inhibitory factor (MIF) signaling and the low-density lipoprotein receptor-related protein-1 (LRP1)-dependent cyclophilin A (CypA)/matrix metalloproteinase-9 (MMP9) axis. LEVOO also helped to restore retinal docosahexaenoic acid (DHA) and dopamine in OIR retinae. In conclusion, LEVOO demonstrated multifaceted efficacy in the intervention of OIR. It reconstructed retinal vasculature, restored retinal function, and rescued neuronal cell loss with strong anti-oxidative and anti-inflammatory effects. Collectively, these findings establish LEVOO as a promising non-invasive complementary strategy for the management of ROP.

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Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Topic: A.06. Developmental Disorders

Support: NIH R01-NS112291-01
Myotonic Dystrophy Foundation

Title: Suppression of Toxic CUG RNA Rescues Molecular and Behavioral Phenotypes in a Brain-Specific Mouse Model of Myotonic Dystrophy Type 1

Authors: *B. BEKELE[1], R. DE DATTA[2], J. D. ARBOLEDA[3], J. P. SCHROEDER[5], E. T. WANG[4], G. J. BASSELL[6];
[1]Emory Univ. Sch. of Med. Neurosci. Grad. Program, Atlanta, GA; [2]Emory Univ., Atlanta, GA; [3]MGM, [4]Mol. Genet. and Microbiology, Univ. of Florida, Gainesville, FL; [5]Emory Univ. Dept. of Human Genet., Atlanta, GA; [6]Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Myotonic dystrophy type 1 (DM1) is a multisystemic disorder associated with cognitive impairment, learning and memory deficits, excessive daytime sleepiness, and neuropsychiatric symptoms. While toxic CUG-repeat RNA and MBNL sequestration are established drivers of disease, progress toward understanding and treating CNS manifestations has been limited by a lack of tissue-specific animal models that enable investigation of disease progression. To address this need, we developed a repressible brain-specific DM1 mouse model expressing 960 interrupted CTG repeats in forebrain neurons. We previously established that these mice recapitulate key features of DM1 neuropathology, including RNA foci accumulation, MBNL dysregulation, alternative splicing defects, molecular alterations in synaptic proteins, and deficits in learning and memory. Using this model, we investigated the reversibility of neuronal pathology and defined the temporal window of molecular recovery following transgene suppression. We first confirmed doxycycline-dependent suppression of transgene expression and a corresponding reduction in nuclear CUG RNA foci. We then assessed restoration of MBNL protein distribution, including recovery of cytoplasmic localization, and evaluated correction of alternative splicing defects in neuronal transcripts at both the RNA and protein levels. Finally, we determined whether reversal of molecular abnormalities was accompanied by improvement in behavioral deficits, including previously observed impairments in contextual and cued fear conditioning. Suppression of CUG-repeat expression resulted in a marked reduction of nuclear RNA foci and restoration of MBNL protein distribution, including increased cytoplasmic MBNL levels. These molecular changes were accompanied by correction of alternative splicing defects in multiple neuronal transcripts implicated in synaptic function and neurotransmission. Importantly, rescue of aberrant splicing was observed at both the RNA and protein levels, including normalization of disease-associated isoform expression patterns. Notably, 8 weeks of doxycycline treatment in adult DM1 mice rescued deficits in contextual and cued fear conditioning, whereas 4 weeks of treatment was insufficient, demonstrating that sustained

suppression of toxic CUG-repeat RNA can restore learning and memory function. Together, these findings demonstrate that key molecular and behavioral manifestations of DM1 remain reversible in the adult brain and inform future therapeutic strategies.

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Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.09/H6

Topic: A.06. Developmental Disorders

Support: NIH Grant P42ES010356

Title: Persistent Neuro-epigenetic Impacts in the Hippocampus after Developmental Exposure of Rats to Cadmium and Benzo[a]pyrene

Authors: S. K. MURPHY[1], A. B. HAWKEY[2], C. WELLS[1], ***E. D. LEVIN**[3];
[1]Duke Univ., Durham, NC; [2]Psychiatry & Behavioral Sci., Midwestern Univ., Downers Grove, IL; [3]Duke Univ. Med. Ctr., Chapel Hill, NC

Abstract: Developmental exposure of Sprague-Dawley rats throughout gestation sc via Alzet 2ML4 minipumps in dams to cadmium (Cd, 0.3 mg/kg/day), benzo[a]pyrene (BaP, 0.03 mg/kg/day), or both was shown in our lab to cause cognitive impairment of the offspring. We assessed effects of these exposures on epigenetic changes in the offspring hippocampus using Reduced Representation Bisulfite Sequencing to identify significantly differentially methylated CpG sites, which were ranked by FDR values and annotated to the nearest gene transcription start site. Taking the top 5,000 CpG sites in each group, we retained gene annotations having ≥10 CpG altered sites, then compared these across groups. There were 7 males and 7 females in each exposure group. The Cd group had 111 genes with ≥10 affected CpGs, the BaP group had 41, and the Cd+BaP group had 30. Most affected CpG sites showed reduced methylation relative to the controls. There were 11 genes in common between the Cd and BaP groups with only three of those being retained in the Cd+BaP group (Cited2, Cacng5 and Ptch1). There was complete overlap of the CpG sites in all three groups for Cacng5, which encodes an AmpA receptor regulatory protein important in synaptic transmission, with the Cd+BaP group adding two additional sites with increased methylation that were not affected in the Cd or BaP groups. For CpG sites associated with Cited2, which encodes a transcriptional coactivator important for development and in hypoxia, the Cd, BaP, and Cd+BaP groups had 20, 55 and 12 affected sites, respectively. The Cd and BaP groups had 18 overlapping sites, and all sites showed decreased methylation relative to controls. In contrast, none of the affected Cited2 sites in the Cd+BaP group overlapped with the single exposure groups, with increased methylation at 10 of the 12 sites. The Ptch1 gene codes for a member of the hedgehog signaling pathway that plays an

important role in embryonic development and is implicated in developmental disorders. The Cd, BaP and Cd+BaP groups had 18, 13, and 12 affected Ptch1 sites, respectively, all with decreased methylation. There were 11 sites overlapping between Cd and BaP groups and all 12 sites in the Cd+BaP group overlapped with either the Cd or BaP groups. Independent analyses of all 111, 41, and 30 affected genes showed enrichment in the Cd group for transcriptional regulators and those involved in neural tube closure; for BaP, Ras signaling and glutamatergic synapse; and for Cd+BaP, bone mineralization, neural tube closure and brain development, respectively. These overlapping and independent effects of Cd, BaP or Cd+BaP exposures on DNA methylation may contribute to the cognitive deficits.

Disclosures: S.K. Murphy: None. **A.B. Hawkey:** None. **C. Wells:** None. **E.D. Levin:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.10/H7

Topic: A.06. Developmental Disorders

Title: Novel mouse models for neurobiology research

Authors: *J. BECKWITH, J. MERRIAM, D. POMERLEAU, C. DAVIS, J. KELMENSON, H. ONDA;
The Jackson Lab., Bar Harbor, ME

Abstract: The Jackson Laboratory (JAX) Repository is a centralized resource of genetically-defined models enabling scientists to investigate neurobiology in normal and disease states - critical aspects of biomedical research and data reproducibility. We will highlight new models for neurological research, and present our genetic quality control results over a three-year period. Several optogenetic mouse lines have been generated that express fluorescent proteins fused to optimized opsins (light-activated proteins that alter membrane potential and allow rapid control of neuronal activity). New lines with GCaMP fluorescence in response to calcium (an indicator of cell activation) include those expressing GCaMP6, GCaMP7, GCaMP8, jRGECO1a and other variants. Chemogenetic mice express designer receptors exclusively activated by designer drugs (DREADDs) inducible with pharmacologically-inert clozapine-N-oxide. Strains for fluorescent tracking of DNA repair pathways, homology directed repair (HDR) and non-homologous end joining (NHEJ) repair events are summarized. Additionally, we characterize intersectional strains that express such effector molecules and/or fluorescent reporters with combinations of Cre-lox, FLP-frt, Dre-rox, and Tet-On/Off functionality.
Upon JAX Repository acquisition of new mouse lines, we perform Genetic Quality Control (GQC) analyses that confirm mutation identity, sample genetic background, and screen for unwanted passenger alleles (*e.g.*, neo, Cre, FLP, GFP, RFP, and other mutations identified in respective publications). For the 1,000+ mouse lines newly acquired from 2023-2025, our GQC steps revealed more than 30% arrived with some unexpected feature ranging in severity from

minor genetic background differences, cryptic aspects of the desired mutant allele, significant deviation from reported congenicity, presence of additional mutant alleles, etc. The most severe examples required considerable corrective measures prior to making the strain available to the scientific community. Because variations in genetic background can significantly affect neurological phenotype, GQC evaluation enhances the likelihood for reproducible results. Researchers may query the collection of models using the JAX Mouse Search website (**mice.jax.org**). This resource includes mice donated by many generous institutions. Researchers are encouraged to donate their mouse lines via a very short online form (**jax.org/donate-a-mouse**). Visit JAX Resources for Optogenetics, Cre-dependent Optogenetic Tools and Cre Strains for Neurobiology (**jax.org/optogenetics**). JAX receives support from NIH, HHMI and private foundations.

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Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.11/H8

Topic: A.06. Developmental Disorders

Support: NIH/NINDS Grant 5R01NS027699-37

Title: Asymmetric Compensation by the ATXN1-Like and ATXN1 Paralogs Confers Robustness to CIC-Dependent Transcriptional Programs in the Embryonic Forebrain

Authors: *E. VILLAVICENCIO GONZALEZ[1], T. GONZALEZ-ROBLES[1], H. LEE[2], A. ENGSTROM[4], Z. YU[1], H. YALAMANCHILI[1], H. CHEN[3], Z. LIU[1], H. Y. ZOGHBI[5]; [2]Mol. Human Genet., [3]Pediatrics, [1]Baylor Col. of Med., Houston, TX; [4]Baylor Collage of Med., Houston, TX; [5]Mol. and Human Genet., Baylor Col. of Medicine/HHMI, Houston, TX

Abstract: Capicua (CIC) is a widely expressed transcriptional repressor critical for neuronal differentiation and function, with pathogenic variants implicated in autism spectrum disorder, intellectual disability, and developmental delay. CIC directly binds DNA to repress target genes and functions in complex with ATXN1 or its highly conserved paralog, ATXN1-Like (ATXN1L). Complete disruption of these complexes in mice, through knockout (KO) of CIC or double KO of ATXN1 and ATXN1L, leads to perinatal lethality due to lung, brain, and gut defects. Interestingly, single KO of ATXN1 or ATXN1L results in viable mice or only partial perinatal lethality, respectively, suggesting some functional redundancy between ATXN1 and ATXN1L, and therefore within their complexes with CIC. Given the well-established requirement for CIC in cortical development, we aimed to define the degree of functional redundancy between CIC-ATXN1 and CIC-ATXN1L complexes in the developing mouse forebrain. To this end, we characterized the transcriptional profiles of CIC, ATXN1, and

ATXN1L single KOs by RNA-seq and mapped the genome-wide DNA binding sites of each of these proteins across wildtype and KO contexts by CUT&RUN. Loss of CIC results in severe dysregulation of hundreds of targets in the forebrain, while the loss of either paralog has a comparatively small effect on the same targets, with ATXN1L KO showing an intermediate effect and ATXN1 KO much milder dysregulation. DNA binding patterns of both paralogs are highly similar, especially in the promoters of canonical CIC targets, consistent with extensive functional redundancy. When either paralog is lost, binding of the remaining paralog increases at shared CIC targets; notably, key cell fate regulators such as ETV4 and ETV5 show greater compensation by the CIC-ATXN1L complex. This establishes that, while both complexes regulate similar targets, the CIC-ATXN1L complex is the predominant regulator of key transcriptional targets during early forebrain development. Overall, this work sheds light on the complexity of paralogous transcriptional cofactors and how functional redundancy buffers critical genetic programs against genetic perturbation.

Disclosures: E. Villavicencio Gonzalez: None. **T. Gonzalez-Robles:** None. **H. Lee:** None. **A. Engstrom:** None. **Z. Yu:** None. **H. Yalamanchili:** None. **H. Chen:** None. **Z. Liu:** None. **H.Y. Zoghbi:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.12/I1

Topic: A.06. Developmental Disorders

Support: Howard Hughes Medical Institute

Title: Evaluating antisense oligonucleotide treatment response in aged female Hnrnph2 mutant mice

Authors: *E. CHU[1,2], R. POLO PRIETO[1,2,3,4], S. MARASINI[1,2,5], E. RIVERA[1,2], A. KORFF[6], H. KIM[6], B. POWERS[7], F. BENNETT[7], H. Y. ZOGHBI[1,2,4,5];
[1]Jan and Dan Duncan Neurolog. Res. Inst., Houston, TX; [2]Dept. of Mol. and Human Genet., [3]Med. Scientist Training Program, [4]Program in Genet. and Genomics, Baylor Col. of Med., Houston, TX; [5]Howard Hughes Med. Inst., Chevy Chase, MD; [6]Dept. of Cell and Mol. Biol., St. Jude Children's Res. Hosp., Memphis, TN; [7]Ionis Pharmaceuticals, Carlsbad, CA

Abstract: *HNRNPH2*-related neurodevelopmental disorder (HNRNPH2-NDD) is a rare X-linked disorder characterized by developmental delay, intellectual disability, seizures, and impairments in language, motor function, learning, and memory. Heterogeneous Nuclear Ribonucleoprotein H2 (HNRNPH2) is a broad regulator of RNA metabolism, and pathogenic variants frequently cluster near the nuclear localization signal, disrupting protein localization and function. Interestingly, *Hnrnph2* knockout mice are phenotypically normal, due to compensation by its paralog *Hnrnph1*. Mechanistically, HNRNPH2 decreases HNRNPH1 protein levels by

promoting alternative splicing events that result in degradation of *Hnrnph1* transcripts. Thus, antisense oligonucleotide (ASO)-mediated knockdown (KD) of mutant *HNRNPH2* may allow for compensatory increase in *HNRNPH1* expression and represents a promising therapeutic strategy. While ASO KD of *Hnrnph2* at younger timepoints can reverse disease-associated phenotypes in male mutant mice, the therapeutic potential of intervention in adult, heterozygous females remains unknown. Because HNRNPH2-NDD predominantly affects females who exhibit mosaicism, it is important to determine whether ASO-mediated suppression of mutant *Hnrnph2* can provide therapeutic benefit in the context of a mosaic brain. Thus, we evaluated ASO efficacy in an aged *Hnrnph2*$^{R206W/+}$ (R206W) mouse model to assess molecular and behavioral responses at a clinically relevant stage of disease progression. During a broad behavior battery, adult female heterozygous R206W mice exhibited a motor learning deficit on rotarod. A second cohort was administered ASO via stereotaxic intracerebroventricular injection. Molecular and behavioral characterization revealed that while *Hnrnph2* transcript and protein levels decreased dramatically in various brain regions, *Hnrnph1* levels were more modestly increased. Consistent with prior observations, heterozygous females exhibited minimal behavioral abnormalities, but those detected did not improve. Among the top 50 differentially expressed genes, ASO treatment normalized expression of 13 genes and partially corrected 10 but shifted expression of 27 genes beyond wild-type levels. These findings suggest that ASO treatment partially rescues transcriptional dysregulation in aged female heterozygous R206W mice but is insufficient to improve motor learning. Given the limited behavioral phenotype of heterozygous females, future studies will evaluate ASO efficacy in aged hemizygous male mice to determine whether therapeutic response varies by sex, disease severity, or age at intervention.

Disclosures: E. Chu: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ionis Pharaceuticals provided the ASO. **R. Polo Prieto:** None. **S. Marasini:** None. **E. Rivera:** None. **A. Korff:** None. **H. Kim:** None. **B. Powers:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **F. Bennett:** A. Employment/Salary (full or part-time):; Ionis Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ionis Pharmaceuticals. **H.Y. Zoghbi:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ionis Pharaceuticals provided the ASO. F. Consulting Fees (e.g., advisory boards); Lyterian, the Column Group, Cajal Therapeutics, Regeneron.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.13/I2

Topic: A.06. Developmental Disorders

Support: T4-AN-04 project funded by Italian Ministry of Health

Title: An Organotypic Cerebellar Model of ATM Deficiency Reveals Cyclin A as a Druggable Readout of Neurodegeneration and suggests a link between HDAC4 Inhibition and Cell Cycle Suppression.

Authors: A. FIDILIO, S. VARRASI, F. CARACI, ***A. G. COPANI**;
Univ. of Catania, Catania, Italy

Abstract: Cerebellar neurodegeneration in ataxia-telangiectasia (A-T) remains without effective therapy. The ATM-deficient *Atm*^{tm1Bal} *(Bal)* mouse model recapitulates neuronal cell cycle reactivation - a proposed upstream driver of Purkinje cell death (Li et al., J Neurosci 2011) - offering a platform for mechanistic screening. Using organotypic cerebellar cultures from postnatal day 12 homozygous *Bal*/*Bal* mice and wild-type littermates, we first characterized the degenerative timeline. After 20 days *in vitro*, we observed no frank neuronal death by LDH release or altered *Bax* expression in *Bal* cultures, indicating a pre-degenerative window suitable for pharmacological intervention. RT-PCR profiling of cell cycle markers revealed no significant difference between genotypes for *cyclin D1* or *p21*. However, *cyclin A* expression was significantly elevated in *Bal* cultures versus controls, establishing it as a sensitive, quantifiable endpoint of aberrant cell cycle activity. We therefore tested whether *cyclin A* suppression could serve as a readout for neuroprotective drug screening. Chronic treatment with ribociclib, a known CDK4/6 inhibitor currently approved for HR^{+}/HER2^{-} advanced breast cancer, fully prevented *cyclin A* upregulation in *Bal* cultures. Extending these findings, we targeted HDAC4, a molecule positioned downstream of ATM and upstream of cell cycle control (Herrup and Chen, DNA Repair, 2013). Using asenapine - an atypical antipsychotic currently approved for bipolar I disorder and recently identified as an HDAC4 inhibitor (Di Stefano et al., Biomed Pharmacother, 2025) - at 10 μM chronically, we observed equivalent suppression of *cyclin A* expression. Notably, Di Stefano et al. reported that asenapine shows higher affinity for HDAC4 than tasquinimod, a known HDAC4 inhibitor that lacks clinical approval or use. These data demonstrate that HDAC4 inhibition phenocopies cell cycle blockade by direct CDK inhibition in ATM-deficient cerebellar slices. We conclude that the *Bal* organotypic culture model, using *cyclin A* as a rapid quantitative endpoint, is useful for identifying neuroprotective compounds acting on the ATM-cell cycle axis.

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Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

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Program #/Poster #: PSTR254.14/I3

Topic: A.06. Developmental Disorders

Support: 5R01MH140184-02

Title: Persistent sensory processing and behavioral atypicalities in a mouse model of neonatal encephalopathy

Authors: *M. KHALIFA[1], S. NARWEKAR[2], A. RIBIC[3];
[1]Univ. of Virginia, Charlottesville, VA; [2]Univ. of Virginia, CHARLOTTESVILLE, VA; [3]Dept. of Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: Hypoxia-ischemia (HI) is common brain damage in neonates, occurring at a rate of 3.5 per 1000 live births in high-income nations and as high as 30 per 1000 live births in low- and middle-income nations. Systemic neonatal HI affects blood flow and oxygenation, causing cerebral palsy, epilepsy, and behavioral and intellectual impairments in up to 60% of survivors. In this study, we induced HI damage in postnatal day 10 (PND 10) C57Bl/6 mice through unilateral carotid ligation followed by 60 minutes of exposure to 8% oxygen, known as the "Rice-Vannucci" model, or through sham procedures. At PND 60, we used the well-established visual associative learning task, followed by dual-brain neural recordings from the visual and prefrontal cortices in the trained mice. Our results showed that neonatal HI mice display an impulsive-like phenotype, with increased response bias and reduced reaction times to reward cues. At the neuronal level, HI mice show impaired selectivity for and representation of task cues in the visual and prefrontal cortices, implicating sensory cue-processing deficits in behavioral impairments after neonatal HI. Indeed, neuronal responses in both the visual and prefrontal cortices were predictive of sham mice, but not of HI mice, suggesting that neonatal HI impairs the association between neuronal activity and behavior. In conclusion, HI has a persistent negative impact on the processing of sensory information cues and an impulsive-like phenotype in the adult mouse.

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Poster

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Topic: A.06. Developmental Disorders

Support: NIH R01-NS112291-01
Myotonic Dystrophy Foundation

Title: Altered Regulation of Synaptic Proteins in a Brain-Specific Mouse Model of Myotonic Dystrophy Type 1

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Abstract: Myotonic dystrophy type 1 (DM1) is a multisystemic genetic disorder. Individuals with DM1 commonly experience cognitive deficits, impaired learning and memory, excessive daytime sleepiness, anxiety, and other neuropsychiatric symptoms that significantly impact quality of life. Despite increasing recognition of these CNS manifestations, the molecular mechanisms underlying neuronal dysfunction in DM1 remain poorly understood. DM1 is caused by a cytosine-thymine-guanine (CTG) repeat expansion in the 3′ untranslated region of the dystrophia myotonica protein kinase (DMPK) gene. The expanded repeat RNA accumulates in the nucleus and forms toxic ribonuclear foci that sequester Muscleblind-like (MBNL) proteins, resulting in widespread dysregulation of alternative splicing. Because alternative splicing plays a critical role in generating protein diversity required for synaptic development, plasticity, and neuronal communication, disruptions in this process may contribute to cognitive and behavioral abnormalities observed in DM1. Given the critical role of alternative splicing in regulating synaptic protein diversity and function, we examined proteins involved in excitatory and inhibitory neurotransmission in a brain-specific DM1 mouse model that expresses 960 interrupted CUG repeats primarily in the cortex and hippocampus. We found altered regulation of the γ2 subunit of the GABAA receptor, including changes in isoform abundance consistent with dysregulated splicing. In addition, mice expressing expanded CUG repeats exhibited increased levels of the NMDA receptor subunit GluN1 and enhanced inclusion of the N1 cassette, a developmentally regulated exon that modulates receptor function. We also observed altered regulation of tau protein isoforms, characterized by an increased abundance of 3R tau which has been linked with neurodegenerative diseases. Moreover, the membrane repair protein, Annexin-A6, is downregulated in both repeat-expressing mice and DM1 patient brain. Together, these findings demonstrate that neuronal expression of expanded CUG repeats leads to alterations in proteins essential for synaptic signaling and neuronal function. Our results provide further evidence that toxic RNA accumulation in neurons is sufficient to drive synaptic changes and establish this brain-specific mouse model as a valuable platform for investigating mechanisms of neuronal dysfunction in DM1.

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Poster

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Title: Modulation of neurodevelopmental gene regulatory networks by miR9-2

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Abstract: 98% of the human genome is comprised of non-coding transcriptional elements; however, the roles and functions of these elements in developmental processes are still poorly understood. In this study, we explored the role of the highly conserved regulatory MicroRNA-9-2 (MiR9-2) in brain development across species. MiR9-2 is often disrupted in 5q14.3 Microdeletion Syndrome, a human neurodevelopmental disorder characterized by developmental delay, epilepsy, ventriculomegaly, and cerebral vascular malformations. These symptoms are attributed to loss of protein-coding genes at this locus; thus, the contribution of MiR9-2 itself to this disorder has received limited attention. To interrogate the regulatory functions of miR9-2 across neural and vascular cell classes, we generated a germline miR9-2 knockout mouse model. miR9-2 heterozygous and homozygous knockout mice frequently present with third and lateral ventriculomegaly by embryonic day (E) 16.5, and heterozygous mice often develop hydrocephalus by postnatal day 21. Broad histological analysis reveals that miR9-2 knockout mice present with intraventricular or subdural hemorrhaging at E12.5, and parenchymal hemorrhaging at E16.5. Single-nucleus RNA-sequencing of knockout mice at E12.5 and E16.5 reveals novel roles of miR9-2 in modulating endothelial gene regulatory networks. This analysis also reveals de-repression of computationally predicted miR9-2 targets that are known developmentally relevant transcription factors in early born neuronal cell classes, including in Cajal-Retzius and radial glial cells. Ongoing work aims to investigate the spatiotemporal dynamics of miR9-2 activity throughout brain development across species by performing spatial transcriptomics on miR9-2 knockout mice as well as attempt to alleviate vascular dysfunction phenotypes via lipid nanoparticle-mediated delivery of miR9-2. Ultimately, this work aims to explore the role of miR9-2 in modulating foundational neurodevelopmental processes and provide insight to future gene therapy tools for human brain diseases and disorders.

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Poster

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Title: Investigating the Effects of Germline Tsc2 Haploinsufficiency on Cortical Development and mTOR Signaling in Mice

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Abstract: Tuberous sclerosis complex (TSC) is a rare genetic neurodevelopmental disorder caused by pathogenic variants in TSC1 or TSC2, resulting in hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1) signaling. Neurological manifestations of the disease lead to developmental delays, neuropsychiatric disorders, and epilepsy. According to Knudson's two-hit hypothesis, individuals inherit a germline mutation in one allele of TSC1/2, while focal brain lesions arise following somatic loss of the remaining functional allele. Here we modified the commonly used Tsc2 FL/FL (Tsc2tm1.1Mjg/J) mouse line to create a new Tsc2 heterozygous (-/WT) and heterozygous/flox (-/FL) lines. With the new -/FL line, animals exhibit germline loss of one Tsc2 allele, like patients with the disease, while the second allele can be removed by Cre-mediated recombination, modeling a second hit.

Mice with one copy of the floxed Tsc2 gene (FL/WT) were crossed with a Cre deleter (Cre/WT) line to generate Tsc2 -/WT offspring carrying a germline deletion of Tsc2. Tsc2 -/WT mice were crossed to Tsc2 FL/FL mice to generate Tsc2 -/FL mice. Adult brains from wildtype and Tsc2 -/WT mice were utilized to assess lamination, vascular morphology, mTORC1 activity (phospho-S6), parvalbumin-positive interneurons, and astrogliosis in the cortex. To confirm viability of the two-hit approach, Tsc2 wildtype (WT/WT), -/WT and -/FL mice were injected with AAV9-Cre-mCherry on P2.

Tsc2 -/WT mice were healthy and exhibited normal cortical architecture without evidence of cortical dyslamination, vascular abnormalities, altered parvalbumin interneuron morphology, or increased astrogliosis. Phospho-S6 immunoreactivity was comparable between Tsc2 wildtype and heterozygous mice. Cortical neurons infected with AAV-Cre exhibited pronounced somatic hypertrophy in Tsc2 -/FL mice relative to Tsc2 -/WT and WT/WT mice.

Our findings support the two-hit model of TSC pathogenesis and are consistent with prior work indicating that loss of a single Tsc2 allele is not sufficient to drive major structural or molecular abnormalities. Future cortical and hippocampal western blot studies as well as quantitative real-time PCR analyses will be conducted to explore compensatory mechanisms that may be active in Tsc2 -/WT mice.

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Poster

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Title: The Effects of Neurodevelopmental Lead Exposure on Skull Formation, Fontanelles Morphology, and XRF-Elemental Analyses

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Abstract: The environment continues to expose developing children to the neurotoxicant lead. As a result, children are inadvertently exposed to an environmental contaminant that causes persistent brain damage. Here we employed the rat model to simulate what happens in the skull formation, fontanelles morphology, and XRF-elemental analyses of calcium and lead in Control (untreated) compared to Early Postnatal (EPN; lead treated) and Perinatal (PERI; lead treated) rat offspring at postnatal days (PND) 2, 7, 14, and 22. The purpose of the study was to provide evidence that early neurodevelopmental exposure to low-lead levels (i.e., 150 ppm in the drinking water) can cause significant alteration in the skull formations of EPN PERI rats compared to Control rats using 3D volumetric surface plots. Further, the fontanelles of the lead treated rats had differing morphologies relative to control. The data currently suggest that the early exposure to lead, regardless of EPN or PERI exposures can cause cortical bone malformations, with differential effects in delays in closure of the fontanelles between PERI and EPN rats, and morphological changes that may constrain brain volume ontogenetically and evolutionarily; thereby, contributing in part to lead induction of neurodevelopmental disorders of skull formation abnormalities.

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Poster

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Topic: A.06. Developmental Disorders

Support: NIH Grant RM1MH138313

Title: Scalable phenotyping of innate auditory behavior across mouse models of neurodevelopmental and psychiatric disorders

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Abstract: Increased research on neurodevelopmental and psychiatric disorders (NPDs) highlights the need for large-scale behavioral phenotyping across genetic models. One major gap is the lack of systematic investigation on NPD-associated mutation effect on baseline, innate auditory-driven behavior. The Washington University Scalable Mouse Assay Center (WU-SMAC) was formed to collect behavioral and genetic data across 100 NPD-associated genes over five years. We joined the consortium to address this gap in auditory phenotyping by developing a non-conditioned auditory place preference assay (APP) that measures innate auditory-driven behavior in adolescent mice. To assess behavioral responses to communication-relevant spectrotemporal structure, we paired an adult ultrasonic vocalization (social call, SC) with a temporally inverted version of the same call (temporally inverted SC, TI-SC). To compare social-call responses with an acoustically salient nonsocial control, we paired a novel SC with a broadband white-noise burst (BBN). Mice aged 6-8 weeks were tested in two successive stimulus-pair blocks in a dark two-compartment arena connected by a central corridor: one block with alternating SC/TI-SC presentations and a second block with alternating SC/BBN presentations. Baseline activity is recorded prior to each block. The assay captures natural, untrained responses to auditory stimuli, measuring multiple behavioral outputs, including approach/avoidance, freezing, and startle, across models with diverse activity levels. However, scaling this approach requires high-throughput acquisition and analysis, as manual scoring is slow, subjective, and low resolution. To support high-throughput implementation, we designed an open-hardware arena and stimulus-presentation system. To eliminate reliance on manual scoring, we developed an open-source analysis pipeline integrating pose-estimation tools such as SLEAP and DeepLabCut with behavior-segmentation tools such as Keypoint-MoSeq and SimBA. APP has been tested across 10 NPD-associated mouse models, including TSC2, SCN1A, FBN1, MECP2, and SHANK3. We are now using APP to generate quantitative auditory-behavioral fingerprints that will support cross-model ranking of phenotypic similarity, identification of shared and divergent auditory behavioral signatures, and cross-validation with downstream WU-SMAC behavioral assays. With 50 cohorts planned over five years, APP provides a standardized and scalable platform for large-scale phenotyping of innate auditory behavior across NPD-associated genetic models.

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Poster

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Support: 1ZIAHD008884-17

Title: Normal variation in brain architecture in healthy zebrafish larvae

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Abstract: Many genetic and environmental perturbations disrupt brain development in highly specific ways, leading to reproducible and circumscribed clinical phenotypes in associated neurodevelopemental disorders. However, some gene mutations are associated with a wide range of phenotypic outcomes. We hypothesize that in these cases, the mutation may decrease the robustness of neural development, rendering it more susceptible to destabilizing influences. As a first step to testing this hypothesis in zebrafish, we have measured the amount of normal variability in the brains of healthy animals. To do so, we imaged brain from 99 six day post-fertilization wildtype Tübingen longfin strain zebrafish larvae and measured the amount of variability in co-raised siblings. Notably, siblings co-raised in a controlled laboratory conditions displayed a mean coefficient of variation of 5.8% in brain size. Because zebrafish wildtype strains are not isogenic, clutches may have differences in genetic background and other experimental factors. To estimate how much variability in brain volume could be attributed to these factors, we utilized a random-intercept mixed-effects model and analysed the residuals. This revealed that 59% of the phenotypic variability in brain volume remained after accounting for measurement error, clutch-specific factors, and differences in growth rate. Our analysis demonstrates that certain regions like pallium, subpallium and hypothalamus, display a larger variability in regional size in comparison to the other regions. Further, by utilizing structural correlation analysis we demonstrated that regions that are closer to each other exhibit more strongly correlated variation in size in comparison to distant regions. These findings establish a framework for future genetic and environmental perturbation experiments that will probe the role of robustness of brain architecture in neurodevelopmental disorders.

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Title: Neonatal sevoflurane exposure leads to persistent neurobehavioral changes and plasma biomarkers of inflammation in infant rhesus macaques

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Abstract: Animal models and human studies suggest that general anesthesia exposure during infancy results in long-lasting neurocognitive impairments. Considering that millions of children each year undergo procedures that require anesthesia, it is important to investigate the mechanism of anesthesia-induced neurotoxicity to ultimately develop ways to protect the vulnerable developing brain. We have previously reported that repeated sevoflurane exposure in rhesus macaques during the first month of life alters emotional responses to an acute stressor and impairs visual recognition memory. We have also shown alterations in peripheral cytokines within 24 hours after anesthesia exposure, as well as altered synaptic ultrastructure in the hippocampus and dorsolateral prefrontal cortex at 4 years of age. The present study sought to examine whether neurobehavioral changes after repeated sevoflurane exposure were linked to persistent alterations in peripheral cytokine biomarkers. Sixteen infant rhesus macaques were randomly assigned to either receive repeated sevoflurane exposure (three 4-h exposures) or served as unexposed controls. At 6 months of age, all animals underwent blood sample collection and an acute stress test. Sevoflurane exposure in infancy increased granulocyte macrophage colony-stimulating factor (GM-CSF: $t[14]=1.97$, $p=0.035$), decreased monocyte chemoattractant protein- 4 (MCP-4: $t[14]=3.14$, $p=0.004$), but did not affect interferon gamma-induced protein 10 (IP-10: $t[14]=0.12$, $p=0.45$) levels at 6 months of age. During the acute stressor, sevoflurane-exposed macaques emitted fewer vocalizations during the most salient threat condition (Group X Condition: $F(2,28) = 4.76$, $p=0.017$), which may be similar to reports of social communication deficits in children with repeated anesthesia exposure. Interestingly, vocalizations negatively correlated with GM-CSF levels ($r=-0.43$, $p=0.035$). Taken together these data suggest that plasma cytokine levels may be useful biomarkers for detecting anesthesia induced neurocognitive changes in clinical studies.

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Poster

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Title: EIF4A2 is a regulator of interneuron development and seizure phenotypes in zebrafish

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Abstract: Neurodevelopmental disorders (NDDs) are common in the global population and can result in global developmental delay, intellectual disability, epilepsy, and autism spectrum disorder. Our prior research demonstrates that pathogenic variants in *EIF4A2* lead to an early onset NDD characterized by epilepsy, hypotonia, and global developmental delay. EIF4A2 is a translational regulator and interacts with multiple genes essential for interneuron progenitor cell development, differentiation, and migration. The specific mechanisms by which EIF4A2 alters neurodevelopment, however, remain largely unknown. Our study aims to understand EIF4A2's role in interneuron development using zebrafish as a model system with the future goal of developing a therapeutic intervention. In this study, we used CRISPR/Cas9 gene editing to create *eif4a2*$^{+/-}$ and *eif4a2*$^{-/-}$ zebrafish. To investigate the motor impairments and seizures seen in individuals with pathogenic *EIF4A2* variants, we assessed motor function and hyperexcitability using the Ramona Optics Kestrel behavioral chamber. To assess primary motor neuron function, tail coil assays were performed on wildtype (WT), *eif4a2*$^{+/-}$, and *eif4a2*$^{-/-}$ zebrafish at 1-day post-fertilization (dpf), revealing a significant increase in bursts in *eif4a2*$^{+/-}$ and *eif4a2*$^{-/-}$ fish compared to WT (WT n=96, *eif4a2*$^{+/-}$ n= 96, *eif4a2*$^{-/-}$ n=47, $P<0.01$). At 7dpf, *eif4a2*$^{+/-}$ and *eif4a2*$^{-/-}$ fish exhibited increased spontaneous and induced seizure-like behaviors compared to WT. These behaviors are classified as whirlpools, convulsions, or posture-loss events by a machine-learning model (WT n= 87, *eif4a2*$^{+/-}$ n= 96, *eif4a2*$^{-/-}$ n=45, $P<0.05$). To evaluate impacts in interneuron development, we utilized a Dlx5a/6a:GFP transgenic line and observed a 30% reduction of GABAergic interneurons in 7dpf *eif4a2* F_0 acute crispant zebrafish compared to WT ($P<0.05$). Additionally, western blot analysis reveals a significant reduction in parvalbumin (PV) protein in 6dpf *eif4a2*$^{-/-}$ larvae (WT n= 8, *eif4a2*$^{-/-}$ n=7, $P<0.05$). In conclusion, zebrafish are a strong model system to study *EIF4A2*-associated NDD, mimicking the epilepsy and motor impairments observed in the human NDD. Both total and PV specific GABAergic interneurons are decreased in these models, suggesting future targets for intervention. This study highlights how rare genetic disorders can elucidate critical pathways important for common neurodevelopmental disorders, helping to identify possible future therapeutic targets for those with both rare and common etiologies of interneuron dysfunction.

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Poster

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Title: Exploring properties of nociceptor electrophysiology in a rabbit model of cerebral palsy pain

Authors: *B. MOLINE[1,2], E. MENA-AVILA[3,2], L. GENRY[1,2], E. REEDICH[1,2], C. KRAMER[1,2], S. MATSON[1,2], M. R. DETLOFF[4,5], K. A. QUINLAN[3,2];
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Abstract: Cerebral palsy (CP) is a movement disorder which often includes abnormalities in muscle tone, spasticity, and pain. People with CP may experience persistent allodynia where normally innocuous stimuli (i.e., a feather) are painfully perceived, and hyperalgesia where painful perception of noxious stimuli is intensified. Despite roughly 80% of people with CP reporting pain, the underlying causes and mechanisms of its occurrence are understudied. Thus, we use an animal model of CP to evaluate changes in nociceptor excitability. In utero hypoxia-ischemia (HI) injury at 70-90% gestation in pregnant New Zealand White rabbits produces kits exhibiting cell death in the brain and spinal cord, muscle stiffness similar to humans with CP, and behavior consistent with mechanical allodynia. To test if nociceptors - sensory neurons involved in detecting and responding to noxious stimuli - are impacted by perinatal injuries, we measure neuron excitability in the dorsal root ganglia (DRGs) from rabbits exposed to prenatal HI or sham surgical procedure, or naïve controls without any intervention. At postnatal day (P)5 and P18, DRGs are isolated and electrical activity was recorded using whole-cell patch clamp. Rabbit DRG neurons contain cells exhibiting firing patterns consistent with nociceptors and light touch, with the former displaying repeated firing (non-accommodating) and the latter displaying singular firing (rapidly accommodating) when stimulated. Neuron classification is based on several properties, including cell diameter, action potential size and duration, firing pattern, and expression of isolectin-B4 (IB4; a marker of mechanical nociceptors) using green fluorescent protein-tagged antibodies. Preliminary findings indicate IB4-positive cells from HI rabbits are hyperexcitable based on resting membrane potential, and current input needed to produce an action potential (I-on). One-way analysis of variance revealed significantly depolarized resting potential in HI compared to sham and naïve controls (mean = -69.5 mV control, -66.444 mV sham, -56.714 mV HI; $p < .05$) and significant reduction in I-on (mean = 13.65 pA control, 27.456 pA sham, -0.543 pA HI; $p < .05$) in P5 HI rabbit IB4-positive cells. With a greater understanding of DRG neuron firing properties and excitability in HI rabbits, we can elucidate how perinatal injuries could impact pain transmission in CP, allowing for identification of safer and more efficacious treatments for pain than those currently available.

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Poster

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Title: A novel machine-learning classification model detects oxidative fiber type transitions in a rabbit model of cerebral palsy

Authors: *C. KRAMER[1], E. REEDICH[1], H. MCCANN[1], S. DROUIN[1], D. SANDERS[1], E. GONZALEZ[1], T. UNG[1], E. MENA-AVILA[1], B. MOLINE[1], L. GENRY[1], J. GLENNON[1], C. QUIROGA[1], C. J. DIDONATO[2], K. A. QUINLAN[1], M. MANUEL[1];
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Abstract: The distribution of slow- and fast-twitch fiber types in a skeletal muscle heavily influences its physiology. Muscle biopsy studies indicate atypical fiber type composition and fiber size variation in children with cerebral palsy (CP), but this has never been systematically evaluated. In this study, we developed a novel machine-learning classification model to perform high-throughput fiber typing of complete transverse muscle sections. Our XGBoost algorithm-based prediction model yielded a balanced accuracy score of 0.89 and a macro F1-score of 0.89, reflecting its ability to robustly predict muscle fiber type from myosin heavy chain (MyHC) isoform immunofluorescence intensities and morphological descriptors. This is the first reported fiber type classifier to consider hybrid fibers, which is a major advance, considering at least 20% of myofibers are hybrid yet they are routinely overlooked due to difficulty in their detection. We used this classification model to define fiber types of more than 7 million myofibers from flexor-extensor muscle pairs in rabbits that experienced hypoxia-ischemia (HI) injury in utero (modeling CP), and typically developing sham rabbits. We observed an oxidative fiber type shift in flexor muscles (biceps brachii and tibialis anterior) of HI rabbits at postnatal day (P)14-20 and P30-32 (weaning age). This altered fiber type composition imparts reduced contractile force and is amenable to sustained muscle activity; it may reflect chronic low-frequency motor unit activation. This work supports prior clinical reports that developmental trajectories of muscle fibers are disrupted in CP.

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Title: Enhanced Spinal Reflex Responses in a Rabbit Model of Cerebral Palsy

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Abstract: Cerebral palsy (CP) arises from perinatal insults and results in motor deficits, primarily spasticity. Early life cortical damage can result in impaired development of spinal circuits, causing disinhibition and hyperreflexia. Measurements of hyperreflexia can include a larger amplitude reflex, altered recruitment, less depression with repeated stimuli (rate dependent depression), and/or more spread (irradiation). The mechanisms of each have never been studied in CP. We hypothesize that cortical impairment reduces dynamic synaptic drive to GAD2+ GABAergic interneurons mediating primary afferent depolarization, allowing less finely tuned control via the afferent pathway. We used New Zealand White rabbits subjected to prenatal hypoxia-ischemia (HI) at 70-90% gestation. At postnatal day (P)1, HI rabbits were classified by Ashworth as affected or unaffected. These were compared with rabbits exposed to prenatal sham surgeries (anesthetic without HI). Experiments were performed in *ex vivo* midsagittal hemisected spinal cords at postnatal day 1-5 from either sex. Stimulation of ventral or dorsal roots evoked monosynaptic reflexes (MSRs) and dorsal root potentials (DRPs), respectively. Irradiation was recorded from segments adjacent to stimulation. HI affected rabbits had hyperreflexia in all measures. HI affected kits had larger MSR amplitudes (548 ± 432, n = 8) than sham (240 ± 140, n = 14) and HI unaffected (170 ± 44, n = 7) kits at 2.5 x threshold (T) ($p < 0.05$ using Tukey's test, HI affected vs HI unaffected and sham). Amplitudes are expressed as % of response evoked at 1.2 xT. MSR recruitment (normalized amplitude by stimulation intensity) was exaggerated in HI affected kits, with a significant intensity group interaction (two-way mixed effects ANOVA, $p < 0.05$) vs HI unaffected and sham. To measure irradiation, DRPs and MSRs were plotted as % of the AUC or peak response of 1st segment (seg) at 1.2 xT, respectively. DRP irradiation is larger in HI affected rabbits in the second seg (420 ± 302, n = 7, $p < 0.05$, Tukey's test) compared to sham rabbits (174 ± 228, n = 15) and HI unaffected rabbits (121 ± 93, n = 7). MSRs in HI affected spinal cords also show more irradiation: with 2.5 xT, 100% of HI affected cords have responses in 4th seg [n = 2] compared to 0% in HI unaffected [n = 3] and 29% in sham [n = 7]. This preliminary data shows HI affected kits have: 1) increased local DRP/MSR amplitude, 2) exaggerated MSR recruitment, and 3) augmented DRP and MSR irradiation. This shows hyperexcitability in the reflex circuit, both locally and across spinal segments. Further studies are needed to determine the cellular and synaptic mechanisms underlying these changes.

Disclosures: E. Mena-Avila: None. **B. Moline:** None. **M. Manuel:** None. **D.J. Bennett:** None. **M. Gorassini:** None. **K.A. Quinlan:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.26/J7

Topic: A.06. Developmental Disorders

Support: TBCK Foundation Pilot Grant

Title: Identification of Molecular Mechanisms and potential genomic compensatory mechanisms underlying TBCK/PPP1R21/C12Orf4-Associated Syndromes

Authors: *V. ZIMYANIN;
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Abstract: TBCK syndrome, caused by autosomal recessive mutations in the TBCK protein, was the first described disease affiliated with defects in the FERRY-protein complex. The FERRY complex, also known as the Five-subunit Early endosome RNA and Ribosome intermediarY complex, is a stable protein complex consisting of TBCK (Tre-2/Bub2/Cdc16 domain-containing kinase), PPP1R21, C12Orf4, Cryzl1, and Gatd1. Further research has shown that FERRY-affiliated syndromes include a spectrum of rare and severe childhood disorders broadly categorized as intellectual disability syndromes (IDS) or encephalo-neuronopathies. Our studies in Zebrafish show that downregulation of PPP1R21, TBCK and C12Orf4 translation by stable morpholino antisense oligos (MO) causes severe defects in early development and morphogenesis. Consistent with their proposed function on endosomes we observe defects in endosomal trafficking of cell adhesion and cell signaling proteins like E-cadherin and β-catenin, leading to mislocalization of those proteins. In contrast to the knock-down, three independent CRISPR based mutants that we generated in the lab, introducing stop codons either N-terminal or in the middle of the PPP1R21 gene, show only mild behavioral phenotypes and are homozygous viable and fertile. In addition, TBCK alleles with a premature stop codon and double mutants carrying the mutated PPP1R21 and TBCK alleles also do not display any strong phenotypes. Similar discrepancy between knock-down (KD) and (premature stop codons) knock-out (KO) approaches have been observed for both TBCK and PPP1R21 in Drosophila. These data strongly argue for the presence of genetic compensatory mechanisms that function to alleviate deletion phenotypes, while abrupt downregulation of the protein results in strong developmental phenotypes. We are currently comparing RNAseq transcriptomes of morphant and mutant embryos to understand molecular mechanism of TBCK/PPP1R21 syndromes and identify potential genetic compensatory mechanisms. We propose that further understanding of such mechanisms in the context of FERRY complex associated diseases will ultimately benefit our understanding of these related syndromes and and will ultimately benefit patients.

Disclosures: V. Zimyanin: None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.27/J8

Topic: A.06. Developmental Disorders

Support: NIH NINDS R01NS107428

Title: KLHL13 dysfunction causes a neurodevelopmental disorder with therapeutic relevance

Authors: *T. AKHTER[1,2], Z. M. AHMED[2,3], S. RIAZUDDIN[4], S. RIAZUDDIN[2,3];
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Abstract: Ubiquitination, a process that targets substrates for proteasomal degradation or nonproteolytic processing, plays a critical role in neurodevelopment, and its disruption is increasingly implicated in neurodevelopmental disorders (NDDs). Kelch-like protein 13 (KLHL13) is a substrate adaptor of the CUL3-E3 ubiquitin ligase complex that regulates mitotic progression through control of Aurora kinase B (AURKB) localization and turnover. We recently identified one frameshift and three missense hemizygous *KLHL13* variants in individuals with NDD characterized by intellectual disability, speech delay, macrocephaly, and behavioral abnormalities. Cellular and biochemical studies demonstrated that disease-associated variants impair mitotic progression, disrupt AURKB ubiquitination and degradation, and induce genomic instability. Consistent with these findings, *klhl13* knockdown in zebrafish resulted in neurodevelopmental and behavioral abnormalities. Notably, pharmacological inhibition of AURKB using the selective inhibitor AZD1152-HQPA restored mitotic fidelity and rescued both cellular and zebrafish phenotypes, implicating dysregulated AURKB signaling as a key pathogenic mechanism. To further define the role of KLHL13 in neurodevelopment, we generated a CRISPR/Cas9-mediated *Klhl13* knockout mouse model. Consistent with the human phenotype, *Klhl13*-deficient mice were viable but exhibited anxiety-like behaviors, reduced exploratory activity, altered white matter integrity, cerebellar cytoarchitectural abnormalities, genomic instability, and dysregulated AURKB expression. Together, these findings establish KLHL13 as a critical regulator of neurodevelopment and provide evidence that aberrant AURKB signaling links KLHL13 dysfunction to NDD pathogenesis. Ongoing studies are evaluating pharmacological AURKB inhibition and AAV-mediated gene augmentation as therapeutic approaches in the *Klhl13* mouse model. Collectively, our results identify the KLHL13-AURKB pathway as a promising target for precision therapeutic intervention in KLHL13-associated NDD.

Disclosures: T. Akhter: None. **Z.M. Ahmed:** None. **S. Riazuddin:** None. **S. Riazuddin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of Maryland.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.28/K1

Topic: A.06. Developmental Disorders

Support: FAPESP 2021/06287-6
FAPESP 2024/00316-2
CNPq 408213/2024-8

Title: Characterization of knockin mice harboring mutant protein disulfide isomerase a3 associated with intellectual disability reveals pathogenic pathways during neurodevelopment and aging

Authors: *D. BILCHES MEDINAS[1], R. PEREIRA[2], P. ROZAS[3], H. BAKER[4], J. DOS PRAZERES[2], L. BARNY[6], L. PLATE[7], L. M. ELLERBY[5], C. HETZ[3];
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Abstract: A recessive mutation in the gene encoding protein disulfide isomerase A3 (PDIA3) has been found to cause severe intellectual disability (ID) in children. PDIA3 catalyzes protein folding in the endoplasmic reticulum (ER), but the pathogenic mechanisms affecting neurodevelopment remain obscure. To understand ID pathobiology, we generated a knockin mouse line harboring mutant *Pdia3* equivalent to the mutation in patients (p.C57Y). Heterozygous animals were bred to generate experimental groups of homozygotes, heterozygotes, and wild-type littermates. Timed breeding was performed to generate E18.5 embryos. Genotyping was done by PCR followed by digestion with Hpy166II. Behavioral studies were conducted using open-field, elevated plus maze, novel object recognition, novel object location, Barnes maze, and three-chamber tests. Bottom-up proteomics was performed followed by bioinformatic analyses using Enrichr and webgestalt.org. Mitochondrial respiration assays in permeabilized hippocampal tissue were conducted in an Oroboros oxygen electrode. IACUC protocol: 283/2023. No homozygous animals were identified in weaned litters, while being present at a higher rate among pups that died after birth. In contrast, analysis of E18.5 embryos identified Mendelian proportions among wild-types, heterozygotes, and homozygotes. These results demonstrated that mutant *Pdia3* is lethal in homozygotes postnatally. Proteomic and bioinformatic analysis of the whole brain of E18.5 embryos predicted abnormal embryo development and embryonic lethality and indicated potentially pathogenic alterations in vesicular transport of the Golgi complex. Behavioral studies in heterozygotes revealed age-related memory and sociability deficits. Proteomic analyses of the hippocampus indicated possible alterations in cellular respiration with aging, but oxygen consumption assays of hippocampal tissue from heterozygous animals showed no differences in comparison with wild-type littermates. Interestingly, OCRL (oculocerebrorenal syndrome of Lowe), a protein also linked to ID and implicated in membrane trafficking at Golgi complex and early endosomes, was found among

the main proteomic hits altered in aged heterozygotes, suggesting that mutant PDIA3 may impact protein sorting. Overall, our work demonstrates that the genetic perturbation in *Pdia3* associated with severe ID leads to dose-dependent effects in neurodevelopment and aging of mice with proteomic alterations converging to protein trafficking at the Golgi apparatus.

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Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.29/K2

Topic: A.06. Developmental Disorders

Support: Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project (2022ZD0214400; J.I.)
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Gerald Choa Neuroscience Institute Research Program Fund (J.I.)

Title: nELAVL phosphorylation by CDKL5 regulates RNA metabolism and condensates communication to promote experience dependent maturation of the visual cortex

Authors: *S. YUAN, Y. ZHU, Z. ZHENG, H. YIP, M. CHAN, J. IP;
The Chinese Univ. of Hong Kong, Hong Kong, China

Abstract: Development of the visual cortex is activity-dependent, and light exposure after eye opening is required for proper formation of the binocular region in primary visual cortex (V1). Disruption of visual pathways can therefore impair cortical development. CDKL5 deficiency disorder (CDD), an X-linked neurodevelopmental disorder caused by mutations in the Cyclin-Dependent Kinase-Like 5 (CDKL5) gene, is one such condition. In addition to diverse neuropsychiatric symptoms, at least 75% of patients with CDD present with cortical visual impairment. However, how CDKL5 mutations lead to neuronal developmental and functional deficits remains unclear. In this study, we established a cortical visual impairment model in Cdkl5 knockout (KO) mice and performed an unbiased phosphoproteomic screen in V1. We identified the neuron-specific nELAVL family (nELAVL2/3/4, also known as HuB/HuC/HuD) as substrates of CDKL5. Because nELAVLs are RNA-binding proteins, we next examined how

their aberrant phosphorylation in CDD affects mRNA expression in mouse V1 using bulk RNA sequencing. We found that several activity-dependent genes are dysregulated in Cdkl5 KO mice. To investigate how CDKL5-mediated phosphorylation of nELAVLs regulates mRNA expression in mouse V1, we observed enlarged cytoplasmic nELAVLs puncta in V1 neurons in Cdkl5 KO mice and in cells expressing nELAVL phospho-deficient mutants. This dysregulation of nELAVL condensates also led to altered composition of P-bodies and stress granules. Functionally, in vivo two-photon calcium imaging revealed impaired orientation tuning in V1 of Cdkl5 KO mice and mice with local viral-mediated nELAVL phospho-deficient mutations. Our results reveal a critical physiological role of CDKL5-dependent nELAVL regulation in activity-dependent refinement of visual cortical circuits.

Disclosures: S. Yuan: None. **Y. Zhu:** None. **Z. Zheng:** None. **H. Yip:** None. **M. Chan:** None. **J. Ip:** None.

Poster

PSTR254: Animal Models of Developmental Disorders Other Than Autism

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR254.30/K3

Topic: A.06. Developmental Disorders

Support: Taconic Biosciences, Academic Grant

Title: Potential effects of D-cycloserine on PV^+ interneurons expression in the prefrontal cortex of the human 22q11.2 deletion mouse model

Authors: M. MYA[1], T. WESSELS[1], J. W. BOGENPOHL[2], D. A. MITRANO[2], *J. BURKET[2]; [1]Program in Neurosci., [2]Biology, Chem. & Envrn. Sci., Christopher Newport Univ., Newport News, VA

Abstract: Schizophrenia and Autism Spectrum Disorder represent two highly polygenic and phenotypically heterogeneous neurodevelopmental disorders whose genetic signatures are composed of common, rare, and de novo risk alleles and copy number variations. Mutations within chromosomal region 22q11.2 correlate with a high prevalence of neuropsychiatric and neurodevelopmental disorders. 22q11.2 deletion syndrome (DS) results in a 1.5Mb or typical 3Mb deletion within this locus and may be involved in complex phenotypes observed within affected individuals. Prior studies show deficits in behavior and decreased parvalbumin (PV) expression within PFC in young adult male 22q11.2 [Df(h22q11)/+] mice suggesting alterations in prefrontal cortex connectivity and possible dysregulation within GABAergic interneuron circuitry. The human 22q11.2 [Df(h22q11)/+] deletion mice display NMDA receptor (NMDAR) hypofunction shown by their behavioral sensitivity to NMDAR antagonists, such as ketamine and phencyclidine (PCP). This study examined the effects of the NMDAR agonist, D-cycloserine (DCS), in 4-6 week old C57BL/6- Del(16Dgcr2-Hira)1Tac (Taconic Biosciences). Specifically, C57BL/6-Del (16Dgcr2-Hira)1Tac mice (n=32) or WT control were administered a 1-week

subchronic dose of the NMDAR partial agonist, DCS, 30 mg/kg, i.p., or saline vehicle. 22q11.2 [Df(h22q11)/+] mice a subset of brains was perfused for immunostaining using PV and WFA lectin antibodies (1:1000); the latter selectively labels neuronal extracellular matrix, perineuronal nets (PNN), which surround PV+ interneurons. Specifically, we quantified expression of parvalbumin (PV+) in areas related to the social-cognitive circuits (medial orbital prefrontal cortex [moPFC], lateral orbital prefrontal cortex [loPFC] and primary somatosensory cortex [S1]). Changes of PV+ in the loPFC expression were significant between WT and Df(h22q11)/+ drug-treated groups, with no differences seen in saline-treated groups. Moreover, differences in PV^+ expression were seen compared across brain regions of loPFC to moPFC that were not observed in WT mice. WFA expression was significantly lower in moPFC compared to loPFC, irrespective of treatment. In preliminary analysis, there were no differences in PV^+ expression between groups in the S1 region. Ongoing analysis is being conducted to look at sex differences within these measures. Overall, these data are important for understanding the role of parvalbumin expression in 22q11.2DS mice at an early developmental timepoint and help identify neurobiological mechanisms related to this deletion syndrome.

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Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.01/K4

Topic: A.07. Development of Neural Systems

Support: The Sasakawa Scientific Research Grant 2026-4046

Title: Phosphatidylinositol with specific acyl chains contributes to thalamic development

Authors: *M. TAKEDA[1], Y. TAKEKOSHI[1], H. UCHINO[2,3], H. KAJIHO[4], T. KOHNO[1], T. SASAKI[4], M. ARITA[2,3], M. HATTORI[1];
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Abstract: The brain contains a wide variety of lipids. Among them, phospholipids exhibit high structural diversity arising from differences in their fatty acyl chain composition. Recent studies have demonstrated that phospholipid-metabolizing enzymes play critical roles in brain development, suggesting that specific phospholipid species may contribute to brain development. However, the spatial distribution and physiological functions of individual phospholipid species in the developing brain remain largely unexplored. In this study, we investigated phospholipid distributions in the developing mouse brain using an advanced mass spectrometry imaging (MSI) technique capable of distinguishing fatty acyl chains. We found that phosphatidylinositol (PI) with specific acyl chains was highly enriched in the embryonic thalamus. To explore the

underlying mechanism, we analyzed the expression patterns of enzymes involved in PI biosynthesis by *in situ* hybridization. We found that CDP-diacylglycerol synthase 1 (CDS1), a rate-limiting enzyme for PI synthesis, was strongly expressed in the embryonic thalamus. We then generated CDS1 knockout (KO) mice using the *i*-GONAD genome-editing method and analyzed lipid distributions in CDS1 KO mice by MSI. We found that thalamic enrichment of the specific PI species was markedly decreased in CDS1 KO mice. These results indicate that the specific PI species is synthesized in a CDS1-dependent manner in the developing mouse thalamus. We also found that the amount of phosphoinositides (PIPs) with specific acyl chains was decreased in the thalamus of CDS1 KO mice. Notably, CDS1 KO mice exhibited mild abnormalities in barrel structures within the primary somatosensory cortex. Taken together, these findings suggest that the CDS1-dependent synthesis of the specific PI species plays important roles in normal thalamic development. This work presents a novel concept that specific phospholipid species are present in specific brain regions and cell types, where they may contribute to the formation and function of neural circuits.

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Poster

PSTR255: Mechanisms of Sensory System Development

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.02/K5

Topic: A.07. Development of Neural Systems

Support: NIH Grant NS106244
NIH Grant EY022730

Title: Four oscillatory modes in a firing rate model of the developing thalamocortex

Authors: *R. A. TIKIDJI-HAMBURYAN[1], M. T. COLONNESE[2];
[1]Sch. of Med. and Hlth. Sciences, The George Washington Univ., Washington, DC; [2]Dept. of Pharmacol. and Physiol., The George Washington Univ., Washington, DC

Abstract: The dominant pattern of organized neural activity during the initial period of sensory thalamocortical circuit formation in rodent visual cortex is the ‘spindle-burst’: a 500ms to 2s oscillation whose frequency increases from ~5 Hz at postnatal day 5 (P5) to 10-15 Hz by P10 before disappearing around P12. Similar oscillations are observed throughout the developing sensory-motor cortex and frontal cortical regions. A homologous activity, the delta-brush, is prominent during late gestation in humans. Despite the central importance of this class of oscillations to developing circuits, their generative mechanisms remain unknown. Published and preliminary data suggest spindle-bursts: (i) emerge in the relay thalamus as a result of the thalamocortical loop and (ii) critically depend on inhibition provided by the thalamic reticular nucleus (TRN).

To understand how changing synaptic weights, dynamics, and delays might contribute to the generation of spindle-burst oscillations, we developed a firing-rate model with two populations (LGN and TRN) connected by direct thalamic interactions and indirect corticothalamic feedback with a delay equal to or exceeding twice the propagation delay (~18ms each, 36ms total). We identified four oscillatory regimes that can generate spindle-bursts. The first corresponds to the classical Wilson-Cowan mechanism, generating ~10 Hz oscillations with an approximately quarter-period phase shift between LGN and TRN. The second arises via a saddle-node bifurcation, also showing a quarter-period shift. In the third regime, oscillations are not intrinsic to the thalamus but driven by strong cortical excitation controlled by thalamic inhibition. Each cycle consists of brief synchronous bursts in LGN and TRN that propagate through the thalamocortical loop to trigger the next cycle. Although activity is nearly synchronous, frequency is set by loop delay (~20-40 Hz). The fourth regime appears when we extend the model with a cortical oscillator that entrains both populations and thus critically depends on cortical inhibition. Preliminary evidence from recordings in the developing thalamus suggests that each of these oscillatory regimes violates one or more characteristics of spindle bursts observed in the developing visual system, perhaps indicating a critical contribution of the biophysical membrane properties of the developing thalamus or cortex to their generation.

Disclosures: R.A. Tikidji-Hamburyan: None. **M.T. Colonnese:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

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Program #/Poster #: PSTR255.03/K6

Topic: A.07. Development of Neural Systems

Support: NIH Grant NS106244
NIH Grant EY022730

Title: State-dependent modulation of functional domains in the neonatal mouse thalamus

Authors: *T. BUSTAMANTE[1], M. T. COLONNESE[2];
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Abstract: The thalamus plays a central role in sensorimotor integration, yet how its functional organization is influenced by motor state during early postnatal development remains unclear. To address this question, we recorded thalamic activity in head-fixed unanesthetized P7-P8 C57BL/6 mice (n=4). Using high-density multi-shank electrophysiology (SiNAPS Pixel Probe; 1024 channels, 8 shanks), we could cover the entire thalamus in 2-dimensions (rostrocaudal and dorsoventral) in a single recording. Recordings were segmented into periods of spontaneous movement (wakefulness) and quiescent epochs (sleep) by nuchal EMG. Depth-resolved correlation analysis of multiunit activity identified spatially contiguous functional domains within individual shanks across each recording. These domains roughly aligned with different

thalamic nuclei identified by post-mortem analysis of electrode tracts. Although movement increased firing in approximately 3/4 of identified domains and decreased it in the remaining 1/4, within-domain coherence increased regardless of firing-rate modulation, revealing a robust motor-state dependence of thalamic synchrony. Preliminary analyses further suggest that movement differentially modulates inter-domain coordination, increasing correlations between some domain pairs while decreasing them between others. Together, these findings indicate that thalamic functional organization is state-dependent as early as P7-P8 and suggest that motor activity and/or arousal state contribute to the emergence of functional domains in the developing thalamus.

Disclosures: T. Bustamante: None. **M.T. Colonnese:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

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Program #/Poster #: PSTR255.04/K7

Topic: A.07. Development of Neural Systems

Support: NIH R01009607
NIH R21DC020560

Title: Self-generated vocalizations activate the developing auditory cortex via an intracortical pathway in newborn mice

Authors: *D. MUKHERJEE, C.-T. CHEN, P. O. KANOLD;
Johns Hopkins Univ., Baltimore, MD

Abstract: The development of the sensory brain relies on early periphery-generated spontaneous neural activity and later sensory-evoked activity. In the auditory system, development is characterized by an early phase of spontaneous activity generated by the cochlea and a later phase of sensory-evoked activity driven by external sounds. However, during development, altricial mammals produce prominent intermittent sounds by self-vocalizations. 'Motor copies' associated with the copious number of self-vocalizations could strongly activate the auditory cortex (ACtx) and contribute to its plasticity. We performed in vivo imaging of the ACtx on both hemispheres in awake mouse pups from postnatal days (P) 8 (before ear-opening) to P14 (after ear opening), while simultaneously recording the pups' spontaneous vocalization. We observed self-vocalization-associated activity in the ACtx across ages, and this activity was stronger than external tone-evoked activity. Vocalization-associated activity was also observed in the ACtx of *Otoferlin*$^{-/-}$ pups with sensorineural hearing impairment, suggesting a top-down source of activation. Retrograde tracing from the ACtx identified labeled cell bodies in the anterior cingulate cortex (ACC) and secondary motor cortex (M2). The ACC/M2 showed vocalization-associated activity that was strongly correlated with ACtx activity during periods of vocalization. Pharmacological inactivation of the ACC markedly reduced self-vocalizations and overall ACtx

activity. Our results provide the first direct functional evidence that self-vocalizations activate the developing ACtx even before the ear canals are open and that this activation reflects a motor command from the ACC/M2. Collectively, these results identify a novel source of early ACtx activity that can shape development and early neural plasticity. Disruption of this activation could affect development and contribute to later-emerging negative cascading effects on communication and cognitive processes as seen in neurodevelopmental disorders.

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Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.05/K8

Topic: A.07. Development of Neural Systems

Support: R01 NS127973
Neuroscience Institute of the UTHSC

Title: Effects of Lmx1 Deficiency on Cochlear Nuclei Development and Auditory Circuit Connectivity

Authors: *I. ISKUSNYKH[1], B. FRITZSCH[2], E. N. YAMOAH[3], V. V. CHIZHIKOV[1]; [1]UTHSC, Memphis, TN; [2]Dept. of Neurolog. Sci., Univ. of Nebraska Med. Ctr., Crescent, NE; [3]Dept. of Translational Sci., Univ. of Arizona, Phoenix, AZ

Abstract: The formation of auditory brainstem circuits is critically dependent on the early specification of progenitor cells. The cochlear nuclei, which are the first central structures in the auditory pathway, originate from different progenitor populations in the embryonic hindbrain. Atoh1 progenitors generate excitatory glutamatergic neurons, while Ptf1a progenitors produce inhibitory GABAergic and glycinergic neurons. Coordinated development of these excitatory and inhibitory lineages is critical for proper auditory circuit formation and connectivity. Previous studies have shown that *Lmx1a* and *Lmx1b* maintain *Atoh1* expression in lower rhombic lip progenitors that give rise to excitatory cochlear nucleus neurons, but their roles in auditory circuit organization remain unclear. To address this question, we analyzed cochlear and vestibular central projections using lipophilic dye tracing in *Lmx1a* knockout mice and *Lmx1a* knockout mice with *Lmx1b* haploinsufficiency. Both mutant mice exhibited an overall reduction of central auditory input, indicating widespread disruption of auditory pathway development. Interestingly, projections to the dorsal cochlear nucleus (DCN) remained relatively preserved, whereas projections to the AVCN were severely compromised, suggesting differential vulnerability of the DCN and AVCN to Lmx1 deficiency. Dye placement at the crossing of the acoustic stria further revealed progressive loss and an abnormal trajectory of the ventral acoustic stria (VAS) in $Lmx1a^{-/-}$ and $Lmx1a^{-/-}$; $Lmx1b^{+/-}$ mice. Fibers in $Lmx1a^{-/-}$ and $Lmx1a^{-/-}$; $Lmx1b^{+/-}$ mice displayed altered routing between the trigeminal tract and restiform body, consistent with

defects in axon guidance and pathway organization. These abnormalities were associated with pronounced disruption of the anteroventral cochlear nucleus (AVCN), the most severely affected subdivision during both embryonic and postnatal stages, with marked reduction and loss of central projections. Together, these findings demonstrate that Lmx1-dependent developmental programs are essential for the proper organization and connectivity of auditory brainstem circuits.

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Poster

PSTR255: Mechanisms of Sensory System Development

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.06/L1

Topic: A.07. Development of Neural Systems

Support: NEI R00 EY034546 to WP
Georgia Tech Smithgall-Watts Early Career Award to WP
NEI R01EY014645 to IF

Title: Auditory motion responses do not develop in the most myelinated region of hMT+ in early blind individuals

Authors: *Y. GAO[1], K. H. CHANG[2], J. A. PYLES[3], I. FINE[4], W. PARK[5];
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Abstract: A variety of studies have suggested that the human middle temporal complex (hMT+), specialized for visual motion in sighted individuals, reorganizes to respond to auditory motion following early blindness. However, hMT+ in early blind individuals is localized functionally by contrasting responses to moving versus stationary sounds. It has never been firmly established whether or not this functionally defined region corresponds to the canonical anatomical location of MT, which is characterized by high myelination. Here, using functional and quantitative MRI, we compared the functional and anatomical localization of hMT+ in early blind individuals. Structural and functional MRI images were collected from 8 sighted (ages 33-72, 4 female) and 8 early blind participants (ages 34-76, 3 female). Quantitative MRI included PDw, MTw, and T1w acquisitions, from which cortical R1 maps defining anatomical hMT+ were derived (Sereno et al., 2013). Functional hMT+ was identified with standard T2* EPI localizer scans, using visual and auditory stimuli in sighted and early blind participants, respectively. Spatial overlap between functional and R1-defined hMT+ was quantified using Dice coefficients. We additionally compared task-based functional connectivity of the functional and anatomical hMT+ regions using an independent auditory-motion dataset.In sighted controls, visually responsive hMT+

substantially overlapped the R1-defined hMT+ (Dice coefficient: mean = 0.48, SD = 0.14, SEM = 0.05). In contrast, auditory-motion-responsive hMT+ in early blind individuals showed significantly reduced overlap with R1-defined hMT+ (Dice coefficient: mean = 0.18, SD = 0.11, SEM = 0.04). This anatomical-functional dissociation was replicated when using an independent myelin-sensitive measure (T1w/T2w). Connectivity analyses further distinguished the two hMT+ definitions. In sighted individuals, functionally defined hMT+ showed stronger connectivity to occipital regions than R1-defined hMT+, whereas the opposite pattern was observed in the early blind group, indicating that the two regions are part of distinct functional networks.Together, these findings indicate that the auditory motion responses that emerge following early blindness are centered outside the most heavily myelinated core of hMT+. Rather than recruiting MT proper — the densely myelinated, motion-selective region that processes visual motion in sighted individuals — cross-modal plasticity appears to engage the surrounding, less myelinated territory of the broader hMT+ cluster.

Disclosures: Y. Gao: None. **K.H. Chang:** None. **J.A. Pyles:** None. **I. Fine:** None. **W. Park:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.07/L2

Topic: A.07. Development of Neural Systems

Support: NIDCD Grant R01DC009607

Title: Layer-specific refinement of spontaneous and sound-evoked activity in mouse auditory cortex

Authors: *R. JUN[1], P. O. KANOLD[1,2];
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Abstract: Spontaneous and sensory-evoked activity shape developing cortical circuits, yet how these activity patterns organize laminar and interlaminar functional activity in the auditory cortex remains unclear. Here, we examined the postnatal development of spontaneous and sensory-evoked activity in awake mouse auditory cortex. Widefield (WF) and two-photon calcium imaging were performed in Thy1-GCaMP6s mice on a fixed-hearing Cdh23 background. Both male and female mice were included. We identified auditory cortical fields using WF imaging and examined neuronal activity within and across cortical layers with two-photon. We measured spontaneous activity from P7–30 and evaluated sound-evoked responses from P12–30. Across development, spontaneous cortical activity became progressively less synchronized, with decreases in the fraction of active neurons, pairwise correlations, and the frequency and duration of spontaneous network events. Tonotopic organization was present at ear opening (P12) and strengthened, particularly in layer 4, consistent with refinement of thalamocortical organization.

In contrast, local frequency heterogeneity increased in layer 2/3 at later developmental stages, suggesting increasing contributions from intracortical circuitry. To examine interlaminar interactions, we simultaneously imaged layer 2/3 and layer 4 using an electrically tunable lens (ETL). Interlaminar signal (SC) and noise correlations decreased across development, suggesting refinement and pruning of interlaminar connectivity. We also observed a strengthening of frequency-specific functional coupling between co-tuned neurons. Overall, these findings demonstrate that the early auditory cortex exhibits broad, highly synchronized activity across cortical layers that progressively refines and decorrelates with age. Our results further suggest that tonotopic organization is present at ear opening and that L4 and L2/3 follow distinct developmental trajectories: L4 shows strengthening of the tonotopic organization consistent with refinement of thalamocortical inputs, whereas L2/3 exhibits increasing local tuning heterogeneity, likely reflecting maturation of intracortical circuitry.

Disclosures: R. Jun: None. **P.O. Kanold:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.08/L3

Topic: A.07. Development of Neural Systems

Support: NIH R01DC018621-01
NSF IOS-1942480

Title: Dissociable effects of acoustical rearing environment on inhibitory circuit coding in zebra finch auditory pallium

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Abstract: The functional organization of the vertebrate auditory system is shaped by experience during early postnatal development. In the zebra finch (*Taeniopygia castanotis*), the acoustical environment of a typical breeding colony has a profound impact on auditory perceptual behavior and cortical responses to conspecific song, but it is not known which components of that complex environment drive which aspects of circuit development. Using five rearing conditions to separately manipulate background noise amplitude, foreground complexity, and social experience, we examined how different features of the social-acoustical environment affected auditory coding in the caudomedial nidopallium (NCM), a cortical-level auditory area. Compared to birds raised with only their families in acoustical isolation, birds raised with increased background noise or foreground complexity had higher firing rates, similar to birds raised in the colony. Background noise primarily increased the discriminability of neural firing patterns, whereas foreground complexity (operationalized as the number of different singers) primarily benefited selectivity. Reductions in pairwise signal and noise correlations reflecting

more independent tuning and less shared variability between neuron pairs were observed only in fully colony-reared birds. Taken together, these results are consistent with a model in which background noise strengthens mutual inhibition between excitatory ensembles, while foreground complexity strengthens connections within ensembles. These findings suggest that the auditory cortex different statistical features of the acoustical environment have separable effects on plasticity of excitatory and inhibitory connections.

Disclosures: R.T. Williams: None. **C. Meliza:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.09/L4

Topic: A.07. Development of Neural Systems

Support: Frontiers of Science, SEHCITI, Mexico
Dirección de Investigación, UDEM Heatlh, Universidad de Monterrey

Title: Analysis of the transition of Sox10 progenitors to Ebf2 cells during the embryonic development of the trigeminal nerve.

Authors: O. A. AJAO[1], E. OLMOS[2], I. MEESTER[3], M. MARTÍNEZ-ESTRADA[6], R. VIDALTAMAYO[4], *V. C. ZOMOSA[5];
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Abstract: The trigeminal nerve processes sensory information from the head and face. The dysfunction of this nerve has been shown to cause migraine and chronic facial pain. The main focus of our current work is to understand the developmental pathways followed by different trigeminal cell populations. Sox10 is the main molecular marker of neural-crest-derived cells and, particularly, of adult Schwann cells that protect and maintain the axons within the peripheral nerves. Additionally, the mesenchymal-endothelial-derived endoneurium, perineurium, and epineurium provide additional protection layers to the axon bundles and create a blood-nerve barrier. The expression of tight junction proteins, such as ZO-1, is essential for the correct formation of this barrier. In an accompanying work, our group shows that ZO-1 endoneural cells of the postnatal trigeminal ganglia and nerves express the transcription factor Ebf2. Here, we used genetically modified 129Sv Ebf2-TauGFP mice that express the histological fusion protein marker tau GFP under the control of the Ebf2 promoter to analyze the embryonic transition of expression of Ebf2 from a Sox10 population to a postnatal ZO-1 endothelial population. Our immunofluorescence results show that at embryonic stages E13.5-E16.5, Ebf2 cells co-express Sox10 within the trigeminal ganglia and nerve anlagen. However, at postnatal stages (P0-P10),

the Ebf2 population no longer expresses Sox10 and shifts to a ZO-1-expressing phenotype. Ebf2 expression within the postnatal peripheral trigeminal system is limited to the regions starting at and distal to the mantle zone that marks the border between the central and peripheral nervous systems. Our findings advance understanding of the roles that Ebf2 plays during embryonic development and cell-fate determination in distinct regions of the nervous system, which could lead to the identification of newer molecular targets for the treatment of chronic pain syndromes.

Disclosures: O.A. Ajao: None. **E. Olmos:** None. **I. Meester:** None. **M. Martínez-Estrada:** None. **R. Vidaltamayo:** None. **V.C. Zomosa:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.10/L5

Topic: A.07. Development of Neural Systems

Support: Frontiers of Science, SEHCITI, Mexico
Dirección de Investigación, UDEM Heatlh, Universidad de Monterrey

Title: Ebf2 is required for the maintenance of an endoneurium phenotype in the peripheral and an excitatory neuron phenotype in the central spinal nucleus of the trigeminal system.

Authors: M. OBREGON[1], B. GAMBOA FLORES[2], E. OLMOS[3], M. QUIJANO GÓMEZ[1], I. MEESTER[4], M. MARTÍNEZ-ESTRADA[6], V. ZOMOSA[5], *R. VIDALTAMAYO[5];
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Abstract: The transcription factor Ebf2 is expressed in neural circuits involved in somatosensory processing within the trigeminal system. However, the precise cellular identities and developmental differentiation pathways of Ebf2-expressing cells in this sensory system remain poorly understood. We characterized the molecular expression patterns of Ebf2-expressing cells in the peripheral trigeminal root, and in the principal (PrV) and spinal (SpV) trigeminal nuclei of postnatal day 10 (P10) heterozygous (HET) and knockout (KO) genetically-modified Ebf2-TauGFP-129Sv mice. Tissue from HET and KO mice models was analyzed using multi-marker fluorescence immunohistochemistry and fluorescence microscopy. Cellular phenotypes were assessed using distinct markers of neuronal (βIII-tubulin, NeuN, VGLUT1, VGLUT2, VGAT), Schwann cell (Sox10), astrocyte (GFAP), and endoneurial (ZO-1) phenotypes. In the peripheral trigeminal root, Ebf2 cells did not co-express either neuronal (βIII-tubulin) or Schwann cell markers (Sox10). Instead, they were identified as endothelial endoneurium-forming cells co-expressing the tight junction protein ZO-1 in HET mice. Remarkably, in KO mice, these

endoneurial cells lacked detectable ZO-1 expression, suggesting a disruption of the properties associated with the endoneurial blood-nerve barrier. In the central nervous system, Ebf2 cells in both PrV and SpV were negative for the astrocytic marker GFAP but positive for the mature neuronal marker NeuN. These Ebf2 neurons exhibited an excitatory glutamatergic phenotype, expressing both VGLUT1 and VGLUT2. In PrV, Ebf2 neurons were surrounded by VGAT-positive perisomatic inhibitory neuropil; whereas in SpV, Ebf2 neurons exhibited both inhibitory inputs and VGAT expression, suggesting localized, complex signal processing. Furthermore, cell segmentation analysis revealed a drastic reduction in Ebf2 cell density within the SpV of KO mice compared to HET controls. Our findings suggest that Ebf2 acts as a critical structural regulator of the peripheral endoneurial barrier and is required to maintain neuronal density in central SpV trigeminal nuclei.

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Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.11/L6

Topic: A.07. Development of Neural Systems

Support: UVA 2024 Double Hoo Award

Title: Dyadic Engagement and Approachability Predicts Infant Neural Response to Social Touch

Authors: *M. TRAN;
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Abstract: Early social touch (non-sexual, affiliative touch) supports preverbal communication, emotional expression, and homeostatic regulation (Cascio et al., 2019; Séassau et al., 2023). Gentle stroking at a rate of 3 cm/sec mirrors the natural mother's default stroking rate (Mateus et al., 2021), and is associated with increased subcortical emotional and sensory neural processing in adult and infant populations (Gothard et al., 2022). Identical stroking through a thin plastic film reduces positive emotional valence, enabling a controlled social vs. nonsocial touch paradigm to elucidate differential neural processing relative to infant temperament and caregiver engagement. Eighteen healthy infants (0-4 months) underwent functional magnetic resonance imaging where they completed a 2x2 block design (social vs. nonsocial × auditory vs. tactile). Social touch consisted of 3cm/sec left shin stroking; nonsocial touch used identical stroking over plastic film. Preprocessing in Fmriprep included motion artifact correction, slice timing, spatial smoothing, high-pass filtering, and standard space registration. Parent-reported infant behavior was assessed via the Infant Behavior Questionnaire-Revised (IBQ-R) approach subscale, and dyadic engagement was coded from a 5-minute parent-infant feeding interaction. Three whole-

brain general linear models in nilearn assessed: (1) social vs. nonsocial touch, (2) IBQ-R approachability, and (3) dyadic engagement as predictors of neural response to social touch. We found greater social>nonsocial touch BOLD response in the right postcentral gyrus, right supramarginal gyrus, left middle cingulate gyrus, right rolandic operculum, and left rolandic operculum. Nonsocial>social touch showed greater BOLD response in the left calcarine cortex, right cuneus, left superior occipital gyrus, and left superior parietal gyrus. Increased dyadic engagement predicted increased left rolandic operculum activation during social touch, while greater IBQ-R approachability was positively associated with increased postcentral gyrus activation. This study is the first to differentiate social from nonsocial touch during infancy using a validated control condition (Tuulari et al., 2017). Researching neural and behavioral pathways involved in social tactile processing underscores the biological foundations of skin-to-skin contact as an early intervention, paving way for more precise care for infants. These findings could potentially serve as biomarkers for social-deficit disorders, facilitating earlier diagnoses and enhancing opportunities for early interventions.

Disclosures: M. Tran: None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.12/L7

Topic: A.07. Development of Neural Systems

Support: NIDCD R21DC016144
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NIDCD R01DC020186
NSF NRT grant 19-22697

Title: Resting EEG power covaries with sensory responsiveness in infants at high and low familial likelihood for autism

Authors: *G. T. PULLIAM[1], J. I. FELDMAN[3], K. DUNHAM[4], D. M. SIMON[1], S. CLARK[2], B. KECELI KAYSILI[1], T. G. WOYNAROSKI[5];
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Abstract: Background: Autism is a neurodevelopmental condition characterized by differences in social communication and repetitive behaviors. Differences in sensory responsiveness are considered diagnostically relevant and may manifest as hyperresponsiveness, hyporesponsiveness, or seeking. One avenue for exploring the neural bases of these differences is resting EEG. Power in resting EEG bands varies in the younger siblings of autistic children (Sibs-autism), who are at high likelihood for a diagnosis of autism, versus the younger siblings of non-autistic children (Sibs-NA), and has been linked with sensory responsiveness in Sibs-

autism at 18 months of age. Objectives: We tested the hypothesis that resting EEG power (a) is associated with broader patterns of early sensory responsiveness in Sibs-autism and Sibs-NA between 12-18 months of age and (b) whether these relations differ according to diagnostic outcome or chronological age. Methods: Analyses were conducted with 48 Sibs-autism and 33 Sibs-NA matched on age and sex who were drawn from a larger longitudinal study. Between 12-18 months, resting EEG was collected, and sensory responsiveness was measured via the Sensory Experiences Questionnaire and the Infant/Toddler Sensory Profile. Aggregate scores for hyporesponsiveness, hyperresponsiveness, and seeking were derived by averaging relevant scores from these measures, following z-score transformation. Diagnostic outcome was ascertained via comprehensive evaluations at 3 years. ANOVA and regression were used to test effects of interest, considering age, likelihood status, and diagnostic outcome as moderators; Johnson-Neyman tests were conducted to determine the point at which moderated relations were statistically significant. Results: There were unconditional relations between beta power (β = .222, p = .048) and gamma power (β = .249, p = .026) and seeking. The relation between delta power and hyperresponsiveness was moderated by diagnostic outcome (β = -5.055, p = .033 for the delta power*outcome product term). The relation between theta power and hyperresponsiveness was moderated by age (β = 4.467, p = .015, for the theta power*age product term) and was significant beyond 15.39 months of age. There was also significant relation between theta power and seeking (β = 4.985, p = .007, for the theta power*age product term) beyond 16.13 months of age. Conclusion: Resting oscillatory power covary with sensory responsiveness, with some relations emerging over the 12-18-month window. Implications for research and practice will be discussed.

Disclosures: G.T. Pulliam: A. Employment/Salary (full or part-time):; Vanderbilt University. **J.I. Feldman:** A. Employment/Salary (full or part-time):; Boystown Research Hospital. **K. Dunham:** A. Employment/Salary (full or part-time):; Harvard University. **D.M. Simon:** None. **S. Clark:** A. Employment/Salary (full or part-time):; Vanderbilt University. **B. Keceli Kaysili:** A. Employment/Salary (full or part-time):; Vanderbilt University. **T.G. Woynaroski:** A. Employment/Salary (full or part-time):; Vanderbilt University.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.13/L8

Topic: A.07. Development of Neural Systems

Support: NIH Grant 5R01EY034617

Title: A multimodal, unsupervised state analysis pipeline for developing mouse pups

Authors: *G. MATTESSICH[1], J. BARNETT[2], R. BATISTA-BRITO[3];
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Abstract: Analyzing animal arousal states is a particularly challenging problem in developing mice, as their immature neurological dynamics create rapidly shifting and imprecise behavioral changes. Classical sleep scoring pipelines in adults tend to classify sleep into fixed Wake/REM/NREM labels from EEG/EMG data. However, methods that are adequate for adults cannot cleanly map onto pup states, as the patterns which underlie behavioral transitions are not fully standardized until adulthood. To address this, we developed an integrated framework to score sleep across postnatal development and avoid the instability and imposition of adult sleep state classification.
Current methods that attempt to approach this can be problematic and resource intensive. For example, manually scored, supervised learning models or feature thresholding methods are prone to human bias and time-consuming. Instead, our model learns latent state representations from behavioral and neural features in an unsupervised manner.
For inputs to the model, we extract synchronized, representative, scope frame-level features from local LFP and behavioral video recordings, including motion, an EMG proxy, delta power, a theta/delta power ratio, and a twitch energy value. We robustly scale features per-animal, then pool values per-day. Then, we use principal component analysis (PCA) to build a low-dimensional feature space capturing dominant axes of variation. We use the PCA space to perform unsupervised, soft clustering with a Gaussian Mixture Model (GMM) that identifies recurring states. From the GMM output, we temporally smooth states with a Hidden Markov Model (HMM) and Viterbi decoding to remove isolated noisy labels (such as single-frame transitions and clustering jitter) for more biologically plausible transitions. We then use per-state fingerprints from feature means to semantically label states into aroused, quiet, and REM-like classifications.

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Poster

PSTR255: Mechanisms of Sensory System Development

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Program #/Poster #: PSTR255.14/M1

Topic: A.07. Development of Neural Systems

Support: NIH Grant 1R15HD114135-01
William and Mary Sophomore/Junior Monroe Scholar Research Grant

Title: Mechanically Induced Calcium Signaling Influences Neural Developmental Programs in Xenopus laevis Embryos

Authors: *S. PHAM[1], G. HUSSEY[2], C. BARE[4], M. S. SAHA[3];
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Abstract: Calcium (Ca^{2+}) signaling is a fundamental regulator of nervous system development, controlling neural induction, progenitor maintenance, neuronal differentiation, migration, and activity-dependent gene expression. Transient Ca^{2+} signals emerge during early vertebrate embryogenesis and function as developmental cues to regulate cell fate decisions and tissue patterning and are involved in mechanisms such as apical constriction and convergent extension. While specific developmental programs are correlated with calcium activity, our goal was to investigate the causal relationship of calcium activity and neuronal development. To investigate this relationship, we developed a mechanical perturbation device capable of delivering a controlled 0.8 mm depression to mid-gastrula stage *Xenopus laevis* embryos. To conduct in vivo Ca^{2+} imaging, embryos at the two-cell stage were bilaterally injected with the genetically encoded Ca^{2+} indicator GCaMP6m. Embryos expressing GCaMP6m were imaged during and following perturbation to characterize mechanically induced Ca^{2+} responses in vivo. Mechanical stimulation was found to consistently elicit localized and propagating Ca^{2+} transients within gastrulating tissues, suggesting activation of mechanosensitive signaling pathways. To determine whether these calcium responses were associated with altered developmental patterning, downstream changes in expression of the neural marker genes *sox2* (SRY-box transcription factor 2) and *tubb2b* (neural beta tubulin) were examined using whole-mount in situ hybridization (ISH). Preliminary findings indicate that mechanical stimulation alters the spatial distribution of these marker genes, suggesting that mechanically induced Ca^{2+} signaling may influence neural specification and differentiation during early gastrulation. To further characterize transcriptional responses to mechanical perturbation, RNA sequencing is being performed to assess global differential gene expression. These findings suggest that mechanosensitive Ca^{2+} signaling plays an important role in coordinating neural developmental programs and cell fate decisions during early nervous system formation in *X. laevis*.

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Poster

PSTR255: Mechanisms of Sensory System Development

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Program #/Poster #: PSTR255.15/M2

Topic: A.07. Development of Neural Systems

Support: NSF IOS- 2230829
Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health under grant numbers P20GM103423 and P20GM104318

Title: A toll-receptor map across regions of structural plasticity in the cricket, Gyllus bimaculatus

Authors: M. W. SWEENEY[1], D. F. GARZA, II[2], J. L.-L. BRADLEY[2], B. A. FRENCH[2], M. MATOS[2], L. M. LEDWIDGE[2], ***H. W. HORCH**[2];
[1]Bowdoin college, Brunswick, ME; [2]Bowdoin Col., Brunswick, ME

Abstract: Structural plasticity is common in developing nervous systems, but rarer after maturation. The cricket, *Gryllus bimaculatus,* displays an unusual level of structural plasticity in the central adult auditory system of the prothoracic ganglion (PTG) after unilateral loss of an ear. In addition, a small group of neuroblasts, which give rise to new interneurons in the mushroom body, are important for learning and memory in the adult cricket. In developing and mature *Drosophila*, some aspects of structural plasticity are mediated by Toll receptors. Multiple conserved Toll receptors have been identified in *G. bimaculatus*, including Toll 6.1, 6.2, 7, and 8. We explored the expression patterns of these Tolls in the adult cricket central nervous system (CNS) and in the developing embryo using hybridization chain reaction *in situ* hybridization. In the developing limb buds and CNS, we identified regions of non-overlapping, complementary Toll stripes, and these patterns shifted across embryonic development. Multiple Tolls were also seen in both overlapping and complementary patterns in the PTG, including at the midline. In the brain, Tolls were expressed in multiple regions, but most strikingly in concentric rings centered on the presumed neuroblasts of the mushroom body. Preliminary data suggests that knocking down individual Toll receptors induces abnormal levels of apoptosis and alters the function of the auditory system. These results hint at the functional role this Toll-receptor map might play in regions of high structural plasticity in the cricket.

Disclosures: M.W. Sweeney: None. **D.F. Garza:** None. **J.L. Bradley:** None. **B.A. French:** None. **M. Matos:** None. **L.M. Ledwidge:** None. **H.W. Horch:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR255.16/M3

Topic: A.07. Development of Neural Systems

Title: Movement explains over 95% of activity in developing somatosensory cortex through sparse population recruitment

Authors: *N. J. SATTLER[1], J. C. DOOLEY[2];
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Abstract: In adults, the neural activity in primary sensory areas is optimized to both detect and represent behaviorally relevant features of the environment. In early infancy, however, the development of these cortical functions is hypothesized to depend on highly structured, self-generated activity. In the developing visual system, this takes the form of retinal waves, whereas in the developing somatosensory system, the spontaneous self-generated activity comes in the form of twitches: rapid movements of the skeletal muscles occurring exclusively during REM

sleep. To determine if twitches play an instructive role in the development of primary somatosensory cortex (S1), we first need a baseline characterization of how twitching patterns drive cortical activation and quantify their overall contribution to early cortical activity. Here, we performed large-scale Neuropixel recordings in the forelimb region of S1 in postnatal day 5 rat pups, with simultaneous high-speed 3D-kinematic tracking of the limbs during sleep. Analyzing over 50 thousand forelimb twitches across more than 20 hours of REM sleep, we find that over 95% of activity can be explained by movement of the contralateral forelimb alone. Response rates generally increase with increased amplitude of forelimb movements and successive bouts of twitching. Although twitches drive the vast majority of early cortical activity, S1 responses are sparse, with individual neurons showing low response rates to single twitches. Collectively, these data establish twitching as the dominant driver of early S1 activity. Current work focuses on how individual neurons are recruited into the broader population response, and how this population-level activity promotes somatosensory circuit development.

Disclosures: N.J. Sattler: None. **J.C. Dooley:** None.

Poster

PSTR255: Mechanisms of Sensory System Development

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Topic: A.07. Development of Neural Systems

Support: CNPq, Grant No. 409156/2024-8
FAPESP Grant No. 2024/22717-9.

Title: Maternal immune activation reduces the intrinsic excitability of Layer 2/3 pyramidal neurons and increases neurotransmitter release of Layer 4-to-2/3 synapses in the mouse primary visual cortex

Authors: *J. B. SILVA[1], G. S. VILAR HIGA[2], F. VIANA[3], F. S. BORGES[4], R. DE PASQUALE[5], H. ULRICH[3];
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Abstract: Maternal immune activation (MIA) is a gestational condition resulting from a maternal infection that causes impaired neurodevelopment in offspring. The MIA model induces disturbances in the organization of the cytoarchitecture of the somatosensory and visual cortex, which correlate with decreased neuronal inhibitory activity. We tested if MIA induces alteration in the intrinsic excitability and connectivity of primary visual circuits. The evaluation of the exploratory behavior of MIA mice did not show any significant differences compared to the PBS group. Electrophysiology analysis of the neuronal excitability indicates alterations in pyramidal

neurons of 2/3 layer of primary visual cortex of MIA mice (P14-16). Changes in the membrane potential (IV curve) and frequency of neuronal firing (IF curve) following current injection are statistically different between the control and the MIA group (IF - $p = 0.0002$; IV - $p < 0.0001$). Such differences in the IV curve between the MIA and control groups might be explained by the decreased membrane potential in the MIA group ($p = 0.0004$) and reduced membrane resistance ($p = 0.0417$). The differences in the IF curve might be explained by increased rheobase ($p = 0.0017$) and AHP depth from the peak ($p = 0.0448$) in the MIA group. Furthermore, the action potentials of MIA mice showed reduced peak voltages ($p = 0.0064$) and amplitudes ($p = 0.0239$). Analysis of evoked excitatory post-synaptic currents (EPSC) indicated that electric stimulation of the L4 excitatory neurons increased the efficiency of the neurons in releasing neurotransmitter vesicles in MIA mice. This is observed by the Pulse4/Pulse1 ratio ($p = 0.0262$), as a progressive decrease in the relative post-synaptic current in MIA. This preliminary investigation supports the hypothesis that early alterations in primary sensory areas may influence the maturation and functional organization of secondary sensory and integrative brain regions, consistent with reports of atypical sensory-association network development in ASD.

Disclosures: J.B. Silva: None. **G.S. Vilar Higa:** None. **F. Viana:** None. **F.S. Borges:** None. **R. De Pasquale:** None. **H. Ulrich:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.01/N1

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIMH/NIH grant R01MH125998
Whitehall Foundation grant 2021-08-077

Title: Molecular Mechanisms of Neuronal Oxytocin Receptor Desensitization

Authors: *H. HOANG, K. GEORGE, M. AHMAD;
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Abstract: Oxytocin is a neuropeptide that plays an important role in social behaviors and has been implicated in disorders such as autism spectrum disorder (ASD), schizophrenia, and anxiety. We identified that oxytocin receptor (OXTR) activation causes its rapid desensitization in multiple mouse brain regions including lateral septum (LS), prefrontal cortex (PFC), and bed nucleus of stria terminalis (BNST). This process involves the recruitment of G protein-coupled receptor kinases (GRK2, GRK3, GRK6), followed by the recruitment of β-arrestin-1 and -2. We found that inhibiting GRK2/3/6 kinase activity impaired neuronal OXTR desensitization and internalization, indicating GRKs are key regulators of OXTR signaling in neurons. GRKs interact with specific docking sites on GPCRs to position themselves for phosphorylation and enable downstream regulation. We have identified GRK docking sites on OXTR and assessed

their role in receptor desensitization. AlphaFold structural modeling and PyMOL analysis were used to predict GRK2 interaction sites on OXTR, which were mutated and validated in HEK293T cells. Agonist-induced OXTR desensitization was assessed using calcium imaging, while bioluminescence resonance energy transfer (BRET) assays measured G protein activity, GRK and β-arrestin recruitment, and OXTR trafficking in HEK293T cells and neurons. Structural analysis revealed interactions between GRK2 and specific residues in the intracellular loop 1 (ICL1), and intracellular loop 2 (ICL2) of OXTR. Mutations at these sites showed impaired agonist-induced OXTR desensitization, reduced GRK2/GRK6/β-arrestin2 recruitment and impaired receptor internalization. Together, these findings identify specific GRK docking sites on OXTR ICL1 and ICL2, revealing their role in receptor desensitization and providing new insight into the molecular regulation of OXTR signaling in neurons.

Disclosures: H. Hoang: None. **K. George:** None. **M. Ahmad:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.02/N2

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant R01 MH131807- 01A1

Title: Brain-wide mapping of vasopressin receptor 1a (avpr1a)-expressing neurons in the mouse brain

Authors: *T. GOOD[1,2], D. KAHN[2], M. SADEGHI ALIABADI[2], N. HINDS[2,1], B. D. ROOD[2,1]; [1]Rowan-Virtua Sch. of Osteo. Med., Stratford, NJ; [2]Rowan-Virtua Translational Biomed. Engin. and Sci., Stratford, NJ

Abstract: Vasopressin (Avp) is a neuropeptide that serves important functions in both the cardiorenal system and the central nervous system (CNS). In the CNS, Avp binds to two primary G-protein coupled receptors, Avpr1a and Avpr1b, with Avpr1a being the most abundantly expressed vasopressin receptor in the brain. Previous research characterized the distribution of Avpr1a receptors in specific brain regions and one study examined mRNA expression throughout the brain. To map Avpr1a-expressing neurons across the brain, we utilized a novel transgenic mouse strain comprised of a cross between Avpr1a-Cre and a tdTomato reporter line (Ai14; Jackson Labs) for fluorescent visualization and characterization of Cre-dependent neuronal populations. Double transgenic mice brains (n=13; 6 male, 7 female) were sectioned at 40μm and stained using immunohistochemistry with a primary antibody recognizing red fluorescent protein. Brain slices were imaged at 10x magnification, and images were preprocessed using ImageJ to optimize signal to noise ratio. Using the WholeBrain R-package, images were registered to corresponding reference plates from the Allen Brain Atlas, cells were counted, and counts were mapped to the atlas locations. Using R, cell counts were combined

with area measurements to calculate cell density (cells/mm^2). We quantified the putative Avpr1a+ cell density across a total of 238 brain regions as defined by the Allen Brain Atlas. Data showed that Avpr1a-expressing cells are found in many brain regions but differ greatly in number and density from region to region and often within a given area. Interestingly, we did not observe sex differences in the Avpr1a cell number despite well documented sexual dimorphism in vasopressin innervation. Furthermore, receptor expression was more pronounced in the thalamus, hypothalamus, striatum, and midbrain. Most notably, the nuclei exhibiting the highest expression densities are functionally implicated in memory consolidation, reward processing, and stress regulation, processes well-established to be under Avp modulation. Taken together, this characterization of Avpr1a receptor expression across the brain establishes a neuroanatomical framework for understanding the circuit-level substrates of Avp-mediated behavior, with direct implications for future functional and translational research.

Disclosures: T. Good: None. **D. Kahn:** None. **M. Sadeghi Aliabadi:** None. **N. Hinds:** None. **B.D. Rood:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.03/N3

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIDDK Intramural Grant ZIADK031116

Title: Mining ultra-large chemical space for next-generation P2Y14 receptor antagonists to treat inflammatory diseases

Authors: *D. P. BROUGHTON[1], S. KURMA[1], M. PAVAN[1], A. PRAMANIK[1], N. I. TARASOVA[2], K. A. JACOBSON[1];
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Abstract: Chronic inflammation is associated with many deadly diseases including diabetes, cardiovascular disease, Alzheimer's, and chronic pain. A promising target for treating inflammation is the P2Y14 receptor (P2Y14R), a Class A G-protein coupled receptor that promotes inflammation upon activation by extracellular UDP-glucose. A few potent and selective ligands, structurally related to the heterocyclic piperidine derivative, PPTN (Merck), have been developed and inhibit the P2Y14R pro-inflammatory signaling, including chronic neuropathic pain, but lack the necessary pharmacokinetic properties to progress through clinical trials. To overcome these limitations, a computer-aided drug design pipeline was employed to discover novel P2Y14R antagonists with comparable potency and selectivity but improved pharmacokinetics. The Rapid Isostere Discovery Engine was used to virtually screen an ultra-large library of 20 billion synthetically accessible compounds, searching for ligands with high

3D-shape similarity to MRS4917, the most potent and selective P2Y14R antagonist available to date. This yielded a focused library of ~700,000 MRS4917 analogues, that were subsequently docked into a recently reported MRS4917-P2Y14R complex model. Twenty top-scoring complexes were refined using two independent 500 ns long MD simulations to assess the proposed binding mode over time. An AI-based scoring method, the Radial Topological Convolutional Neural Network (RTCNN), analyzed the range of binding poses sampled for each ligand and ranked compounds for synthesis. The five compounds with the best mean scores were selected for synthesis using palladium-catalyzed fragment assembly techniques, and ligand binding to the P2Y14R is being evaluated using a whole cell fluorescence binding assay. Among the target compounds, modest P2Y14R affinity has been demonstrated.

Disclosures: D.P. Broughton: None. **S. Kurma:** None. **M. Pavan:** None. **A. Pramanik:** None. **N.I. Tarasova:** None. **K.A. Jacobson:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.04/N4

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIDA R01 DA060724
NIDA R01 DA057346

Title: Acute fentanyl and xylazine co-application decreases excitability in HIV Tat-transgenic hippocampal CA1 neurons.

Authors: *R. M. SCHMITT[1], V. YAROTSKYY[2], P. E. KNAPP[3], K. F. HAUSER[2]; [2]Pharmacol. & Toxicology, [3]Dept Anat & Neurobio., [1]Virginia Commonwealth Univ., Richmond, VA

Abstract: Fentanyl, a potent synthetic opioid and a leading cause of overdose deaths, is often combined with α2-adrenergic receptor agonist adulterants such as xylazine. Although morphine and other opioids can exacerbate neuro-acquired HIV, preliminary findings suggest fentanyl ± xylazine promote greater neuroHIV pathology than other opioids. An HIV-1 Tat transgenic mouse model was used to investigate how fentanyl and/or xylazine ± Tat might impair CA1 pyramidal neuronal function using patch-clamp recordings from *ex vivo* hippocampal slices. Acute fentanyl (100 nM) or xylazine (10 μM) application did not affect the pattern or frequency of firing. In contrast, acute fentanyl and xylazine co-application decreased neuronal firing frequency in both Tat^- and Tat^+ mice. Specifically, fentanyl and xylazine co-exposure decreased the firing rate of CA1 pyramidal neurons in Tat^- mice to 100-500 pA stimuli (n=9,p<0.05, Welch's paired t-test) and decreased the amplitude of the action potentials (n=9,p<0.05, Welch's paired t-test). Similarly, fentanyl and xylazine co-application caused a rightward shift in the firing frequency, decreasing the sensitivity of Tat^+ CA1 pyramidal neurons to 75-400 pA stimuli

(n=8, p<0.05, Welch's paired t-test). The current causing half-maximum firing frequencies increased from 107.97 ± 13.34 pA in control recordings to 137.50 ± 18.14 pA in fentanyl and xylazine co-exposed Tat^+ slices, which was not observed in co-exposed Tat^-slices, suggesting Tat interacted with fentanyl and xylazine to dramatically inhibit pyramidal neuronal excitability (n=8, p<0.05, Welch's paired t-test). These results suggest that: (i) fentanyl and xylazine uniquely interact to inhibit hippocampal CA1 neuronal firing in Tat^- and Tat^+ mice, and (ii) HIV Tat exacerbates the inhibitory actions of fentanyl and xylazine in CA1 neurons. We propose that fentanyl, xylazine, and HIV Tat interactions underlie the significant deficits in learning and memory associated with opioid use disorder and HIV comorbidity.

Disclosures: R.M. Schmitt: None. **V. Yarotskyy:** None. **P.E. Knapp:** None. **K.F. Hauser:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.05/N5

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Center for Medicinal Cannabis Research Project P64-05-002

Title: Cannabis-Derived Terpenes Modulate Molecular Pharmacology of Endocannabinoids

Authors: *W. GREENE[1], E. WHITEHOUSE[3], P. R. O'NEILL[2], C. M. CAHILL[3];
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Abstract: Introduction
The legalization of medicinal cannabis has increased interest in the pharmaceutical possibilities of this drug due to scientific and anecdotal evidence of its pain-relieving properties. While the most abundant compound found in cannabis, Δ9-tetrahydrocannabinol (THC), is considered the primary constituent responsible for its analgesic actions, other components such as terpenes are being studied for potential pain relieving effects due to their nonaddictive and nonpsychomimetic properties. This study aims to characterize the molecular pharmacology of the two most abundant terpenes in cannabis, myrcene and β-caryophyllene (BCP).
Methods
We employed an in vitro model in HEK293T cells to study the activity of terpenes at the cannabinoid receptors CB1 and CB2 using the TRUPATH assay. Cells were transfected to express human (hCB) or mouse (mCB) CB1 or CB2 receptors, along with Alpha-i1-RLuc8, Beta3, and GFP2-Gamma8. Five baseline bioluminescence resonance energy transfer (BRET) measurements were taken, followed by the addition of varying doses of endocannabinoids anandamide (AEA) and 2-Arachidonoylglycerol (2AG) with or without the terpene or vehicle, followed by ten additional BRET measurements. Separate groups included dose-dependent

effects of terpenes alone with both hCB and mCB receptors. The BRET ratio is calculated as the acceptor divided by the donor emission signal. We computed delta BRET as the change in BRET relative to the mean of the five baseline BRET measurements. Each condition was performed in triplicate. Data was analyzed by either repeated measures or a 2-way ANOVA.
Results
We found that BCP does not directly agonize hCB or mCB receptors, while myrcene appears to be an agonist of only hCB1. BCP modulates the activity of AEA at hCB1 but not hCB2, and of 2-AG at both receptors by inducing a shift left in the dose response curve, increasing the potency of these endogenous ligands at the cannabinoid receptors. In the mouse receptors, BCP does not modulate the activity of AEA at either mCB1 or mCB2, but does shift the curves left for 2-AG at both receptors. Myrcene appears to modulate the activity of AEA at hCB1, but not of 2-AG or at any other receptor.
Conclusions
Based on these data, it appears that myrcene and BCP act as positive allosteric modulators, which may account for the antinociceptive effects observed in preclinical in vivo research. This work expands the cannabis analgesia literature to include terpenes as a potential new avenue for chronic pain therapeutics. Ongoing research is needed to determine brain regions and cell types involved, as well as to characterize BCP and myrcene modulation of exogenous cannabinoid activity.

Disclosures: W. Greene: None. **E. Whitehouse:** None. **P.R. O'Neill:** None. **C.M. Cahill:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.06/N6

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Synthetic cannabinoid-elicited high efficacy in canonical and non-canonical signaling: Potential mechanisms for toxicity

Authors: *H. YANO, S. OH, C. LUCAJ, R. GUO;
Northeastern Univ., Boston, MA

Abstract: Despite the strict scheduling as banned substances, synthetic cannabinoid (SC) use remains a public health problem. Legalization of cannabis use in many states has not led the noticeable decrease in SC use as originally predicted. In adolescents, vaping of SC has steadily increased in recent years. Since “cannabinoid” implies the effects similar to cannabis, users may unknowingly experience serious adverse effects, which are typically absent with cannabis use. Many SCs are aminoalkylindole molecules distinct from the naturally occurring psychoactive phytocannabinoid, (−)-*trans*-Δ^9-tetrahydrocannabinol (THC) found in cannabis. The adverse toxic effects result in neuropsychiatric (e.g., anxiety and hallucinations), cardiovascular (e.g.,

tachycardia and hypertension), and neurological (e.g., hypothermia, catatonia, and seizure) outcomes, including coma and sudden death. Despite the wide range of toxic effects, the underlying mechanisms remain unidentified. THC is an established partial agonist at cannabinoid CB1 receptors, whereas SCs are reported by others and us to demonstrate much higher efficacy and potency at this site, which likely relates to a much higher incidence of adverse effects. Moreover, some SCs exhibit maximal efficacy at CB1 receptors exceeding that seen with typical full agonists, a phenomenon termed "superagonism." We hypothesize that superagonism plays a major role in these toxic effects. We first characterized currently abused, structurally diverse SCs using a series of bioluminescence resonance energy transfer (BRET) assays and identified different degrees of efficacy within superagonism. The structure-activity-relationships of head, core, and tail modules within these recent SCs were further investigated. Their varied high efficacies were also confirmed neurophysiologically in hippocampal brain slices through CB1 receptor-mediated inhibition of glutamate release. Using a thorough mutational approach targeting the binding pockets as well as conformation-propagation domains, mechanisms of SC-mediated high-efficacy receptor activation were elucidated and differentiated from those of lower-efficacy agonists. Finally, we also found that SCs activate non-canonical transducers at high levels and performed mutagenesis for mechanical understandings. Overall, the high efficacy at both canonical and non-canonical signaling of CB1 receptors in the brain and other organs may underlie the molecular basis of toxicity in SC use. Beyond SC mechanisms, these findings also provide insights into GPCR superagonism and CB1 receptor functions when overdriven.

Disclosures: H. Yano: A. Employment/Salary (full or part-time):; Northeastern University. **S. Oh:** None. **C. Lucaj:** None. **R. Guo:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.07/N7

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant DAR37060149

Title: Mu-opioid receptor-dependent inhibition of noradrenaline synaptic transmission in the mouse dorsal raphe nucleus

Authors: *A. GUGEL[1], J. GIOFFREDI[1], S. C. GANTZ[2];
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Abstract: Opioid use disorder (OUD) and opioid-related overdose are current crises in the United States. The development of synthetic opioids, used for pharmacological pain treatment and recreationally, has contributed to OUD and overdose deaths. The primary site of action for most synthetic opioids is the mu-opioid receptors. These receptors are Galphai protein-coupled receptors that are expressed throughout the brain, and when activated, can inhibit the release of

noradrenaline from locus coeruleus (LC) terminals. This decreased noradrenaline transmission is one driver of sleep and relaxation. Previously, we have shown that LC axon terminals innervate the serotonin nucleus, the dorsal raphe, where the release of noradrenaline mediates alpha1-adrenergic receptor (alpha1-AR)-dependent excitatory postsynaptic currents (alpha1R-EPSC). The serotonin neurons of the dorsal raphe are chemosensitive; upon CO2 exposure they increase their firing. This response aids in homeostasis through projections to the breathing nuclei in the brainstem. Mu-opioid receptor-mediated inhibition of noradrenaline transmission has not been established in the dorsal raphe. Disruption of noradrenaline and serotonin signaling may be partially responsible for prolonged sedative effects of opioid and contribute to overdose. Our work examines the mu-opioid receptor-mediated inhibition of noradrenaline synaptic transmission in the dorsal raphe. Using whole-cell patch-clamp electrophysiology from serotonin neurons in acute mouse brain slices, we found that activation of mu-opioid receptors with an agonist, DAMGO, decreased the amplitude of the alpha1R-EPSC by ~50%. Further, application of DAMGO induced an outward current in a small population of serotonin neurons, suggesting that subpopulation of serotonin neurons may be inhibited directly by postsynaptic mu-opioid receptors. The dependence of mu-opioid receptor-mediated inhibition on the membrane potential of noradrenaline axon terminals will be discussed. Together, the data demonstrates that mu-opioid receptors inhibit the excitatory signaling in the dorsal raphe by 1) inhibiting noradrenaline release and 2) postsynaptically inhibiting a subpopulation of serotonin neurons. Growing our understanding of this molecular circuit is important to improve our understanding of the mechanisms driven by synthetic opioids that could contribute to prolonged and harmful sedation. This would allow for the development of better treatments and interventions for both OUD and opioid-related overdose, when naloxone itself is ineffective in reversing overdose.

Disclosures: A. Gugel: None. **J. Gioffredi:** None. **S.C. Gantz:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.08/N8

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: K01MH123757
R01MH120212

Title: Striatal Primary Cilia as a Dopaminergic cAMP-PKA Signaling Compartment

Authors: R. R. FAGAN[1], J. X. HE[2], M. VON ZASTROW[3], ***A. T. EHRLICH**[4];
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[4]Univ. of California, San Francisco, San Francisco, CA

Abstract: Dopamine signaling through D1 receptors (D1R) in striatal medium spiny neurons (MSNs) is critical for motivation and learning, and its dysregulation underlies psychiatric and

movement disorders including schizophrenia and Parkinson's disease. Despite longstanding therapeutic interest in bidirectionally controlling D1R activity, direct D1R agonists suffer from narrow therapeutic windows, rapid tolerance, and peripheral side effects. A fundamental barrier has been the absence of a subcellular framework explaining how D1R signal transduction is spatially organized in MSNs. Using rat striatal neuron cultures, we show that MSN primary cilia, specialized receptor-enriched signaling organelles extending from the neuronal soma, are physically apposed to dopamine axon terminals, positioning them to receive dopamine during phasic release. Two co-expressed Gs/olf-coupled catecholamine receptors, β1AR and D1R, accumulate in cilia to different degrees, with D1R preferentially concentrated in this compartment. To dissect the relative contributions of ciliary versus plasma membrane receptor pools to cAMP-PKA signaling, we developed compartment-targeted signaling blockers. Both receptors generate cAMP and activate PKA from the cilium; however, cilium-enriched D1R accounts for nearly all D1R-dependent PKA signaling in MSNs, identifying the primary cilium as the dominant site of somatic D1R-PKA signal transduction. We further show that a pool of PKA is anchored at the basal body and, using confocal and lightsheet microscopy, that this pool can be fully mobilized by supraphysiological stimulation, suggesting the cilium is a privileged signaling environment uniquely leveraged by D1R. Together, these findings establish the striatal neuronal primary cilium as a critical subcellular site for neuromodulatory receptor organization of PKA signaling.

Disclosures: R.R. Fagan: None. **J.X. He:** None. **M. Von Zastrow:** None. **A.T. Ehrlich:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.09/O1

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: PAPIIT (DGAPA-UNAM) IG200126
CVU 1104803

Title: Feedback and feedforward muscarinic autoreceptors in striatal cholinergic interneurons

Authors: *Y. PARRADO[1], A. ORTEGA[3], M. PADILLA[5], A. FUENTES-SERRANO[2], D. TAPIA[4], E. GALARRAGA[6], J. BARGAS[7];
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Abstract: Choline acetyltransferase (ChAT) expressing cholinergic interneurons (CINs) comprise a small subset (1 to 3%) of the total neuronal population in the striatum (Str), where they are the only non-GABAergic neurons, responsible for providing most of the striatal acetylcholine (ACh), suggesting that they are a key regulator in the striatal circuitry. Previous studies show that muscarinic M_2-class receptors (M_2/M_4) CINs down regulate calcium currents (I_{Ca}) through $Ca_V2.1$(N) and 2.2 (P/Q) channels. However, a subset of them (30 - 88%) alternatively or concurrently express M_1 receptor mRNA. The action of these receptors on CINs I_{Ca} is the aim of this work. From ChAT-Cre transgenic mice, acutely dissociated CINs I_{Ca} whole-cell recordings, together with specific muscarinic receptors agonists and antagonists, showed that in 37% CINs, the M_1 class receptors up-regulates I_{Ca},, having the rest a predominant M_2-class receptor action: an I_{Ca} downregulation. It is concluded that both autoreceptor classes are functional in neostriatal CINs.

Disclosures: Y. Parrado: None. **A. Ortega:** None. **M. Padilla:** None. **A. Fuentes-Serrano:** None. **D. Tapia:** None. **E. Galarraga:** None. **J. Bargas:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.10/O2

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH R01 NS147337
NIH R01 NS123711

Title: Muscarinic acetylcholine receptors generate spike-independent calcium transients in neocortical somatostatin-expressing interneurons

Authors: *B. ATHUKORALA ARACCHIGE EDWARD[1], D. KANIGOWSKI[2], O. TAKACS[2], N. SHARIF[2], A. L. BARTH[1];
[1]Biol. Sci., [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Somatostatin-expressing (SST) interneurons play a critical role in regulating cortical circuit excitability and sensory processing. Cholinergic signaling through muscarinic acetylcholine receptors (mAChRs) modulates SST interneuron firing, and in vivo Ca++ imaging studies indicate that SST interneurons can be activated during arousal, when acetylcholine (ACh) levels are elevated. However, the contribution of spike-dependent and spike-independent signaling to Ca++ transient detected using genetically-encoded Ca++ indicators has not been well-established. Using GCaMP6f Ca++ imaging and electrophysiological recordings in acute brain slices from mouse somatosensory cortex, we found that puff-applied ACh was sufficient to significantly increase GCaMP6f fluorescence in a subpopulation of SST interneurons, in the presence of TTX to block action potential firing. Pharmacological blockade of mAChRs using bath application of antagonists could abolish this ACh-driven increase in GCaMP6f

fluorescence. Thus, fluorescence transients in SST interneurons can be associated with activation of mAChR-related G-protein coupled signaling pathways, triggering release of Ca++ from intracellular stores. These findings identify a mechanism by which cholinergic neuromodulation can potentially enhance GCaMP fluorescence in SST interneurons, independent of changes in spiking output. These data may be relevant in inferring spiking activity from fluorescence transients in cortical interneurons during in vivo imaging.

Disclosures: B. Athukorala Aracchige Edward: None. **D. Kanigowski:** None. **O. Takacs:** None. **N. Sharif:** None. **A.L. Barth:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.11/O3

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: 5R35GM133802-07

Title: Voltage-gated sodium channel activation by the G_q-coupled neurokinin-1 receptor

Authors: *A. LI, M. R. BANGHART;
Neurobio., UCSD, La Jolla, CA

Abstract: G protein-coupled receptors (GPCRs) are critical mediators of 'slow' neuromodulation, but our understanding of G_q-coupled receptors' effects on neuronal excitability remains incomplete. In cholinergic interneurons (CINs) of the dorsal striatum, the neurokinin-1 receptor (NK1R) is thought to open a tetrodotoxin (TTX)-insensitive Na^+ channel, but the precise molecular identity of this channel is uncertain. To investigate NK1R signaling, we made electrophysiological recordings from striatal CINs in acute brain slices taken from male and female P28-90 C57BL/6 mice, and stimulated receptors using a photoactivatable substance P (SP) developed by our lab. Critically, the use of photopharmacology enables us to observe immediate, potentially transient phenomena following rapid receptor activation. We found that SP, via NK1R, activates a large excitatory current through a G protein-dependent pathway, requiring IP_3R-mediated Ca^{2+} release and protein kinase C (PKC) activation. We hypothesized that NK1R couples to the Na^+ leak channel NALCN in these cells, but instead found a major role for transient receptor potential, canonical (TPRC) channels. Unexpectedly, the SP-evoked current also includes a TTX-sensitive component, implicating NK1R activation of voltage-gated sodium channels (VGSCs) through a PKC-dependent mechanism. To our knowledge, this is the first reported instance of VGSC activation by a G_q-coupled receptor, representing a new mechanism by which GPCRs shape neuronal excitability.

Disclosures: A. Li: None. **M.R. Banghart:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.13/O5

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Roy J. Carver CHaritable Trust Early-Stage Investigator Award
Alfred P. Sloan Foundation Research Fellowship in Neuroscience
NIDA/NIH R37DA060149

Title: Protein kinase C decreases alpha-1 adrenergic receptor-dependent synaptic transmission in the central nervous system

Authors: *H. RUST[1,2], J. A. CARUANA[1], M. R. BANGHART[3], S. C. GANTZ[2];
[2]Mol. Physiol. & Biophysics, [1]Univ. of Iowa, Iowa City, IA; [3]Neurobio., UC San Diego, La Jolla, CA

Abstract: Alpha 1-adrenergic receptors (α1-A_R) are G protein-coupled receptors highly expressed in the autonomic and central nervous systems. While the physiological role of α1-A_R is well-characterized in smooth muscle innervated by the sympathetic nervous system, these receptors are also prevalent in the brain where their activation induces synaptic plasticity and mediates excitatory neurotransmission. In cell lines and heterologous expression systems, protein kinase C (PKC) phosphorylates α1-A_R and decreases receptor activity, primarily via receptor internalization or desensitization. Whether PKC decreases α1-A_R activity in the brain is not known. Here, we used whole-cell patch-clamp electrophysiology from serotonin neurons in acute mouse brain slices containing the dorsal raphe nucleus. Electrical stimulation of the brain slice causes the release of noradrenaline from axon terminals which activates α1-A_R and produces an α1-A_R-dependent excitatory postsynaptic current (α1-A_R-EPSC). Activation of PKC with a phorbol ester, PDBu, eliminated the α1-A_R-EPSC. When α1-A_R-dependent inward currents were evoked by photolysis of caged-noradrenaline (I-NA), application of PDBu also eliminated I-NA, indicating that activation of PKC eliminated the α1-A_R-EPSC through a postsynaptic mechanism and not through a decrease in noradrenaline release. In contrast to the effect of PDBu, activation of PKC with another phorbol ester, PMA, had little effect on the α1-A_R-EPSC and I-NA. The decreased efficacy of PMA compared to PDBu may be related to stronger lipophilicity of PMA which causes greater activation of PKC within the plasma membrane compared to the cytosol. The effect of endogenous activation of PKC on the α1-A_R-EPSC and the role of α1a-A_R and α1b-A_R will be discussed. Together, the results demonstrate that PKC is a negative regulator of α1-A_R activity in the central nervous system.

Disclosures: H. Rust: None. **J.A. Caruana:** None. **M.R. Banghart:** None. **S.C. Gantz:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.14/O6

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: Opioid-mediated suppression of hippocampal interneurons during learning and memory

Authors: *A. CACCAVANO;
NIH/NICHD, Washington, DC

Abstract: Opioid receptors within the central nervous system regulate pain sensation and mood and are key targets for drugs of abuse. Within the hippocampus, mu-opioid receptors (MORs) are enriched in inhibitory parvalbumin-expressing interneurons (PV-INs), with MOR agonists suppressing PV-IN activity. PV-INs critically regulate hippocampal activity important for learning and memory, yet it is unknown how opioid-mediated neuromodulation of PV-INs alters this activity. We observed that PV-IN mediated inhibition is robustly suppressed by opioids in acute hippocampal slices from mice, nonhuman primates, and humans. This hippocampal disinhibitory motif was established in early development, when immature PV-INs and opioids were found to regulate early population activity. In adulthood, acute opioid-mediated modulation was partially occluded with morphine pretreatment, with implications for the effects of opioids on hippocampal network activity important for learning and memory. Ongoing in vivo 2-photon calcium imaging experiments are exploring a functional role for opioids in altering microcircuit function and spatial learning and memory. Together, these findings demonstrate that opioids exert a targeted modulatory effect on hippocampal PV-INs that is established in early development and conserved across evolution.

Disclosures: A. Caccavano: None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.15/O7

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural Funds of the National Institute on Drug Abuse
Robert and Sherrie Frankel Postdoctoral Fellowship in RLS Research

Title: Allosteric modulation of μ-opioid receptor heteromers: Implications for opioid drug discovery

Authors: *G. ENTEN[1], N. LLOPART[2], A. ALONSO-CARRASCO[2], M. CIRUELA JARDI[2,3], M. VALLE LEON[1], N. CAI[1], C. J. EARLEY[4], S. MORENO[2], V. CASADÓ ANGUERA[2], L. PARDO[3], V. CASADÓ[2], S. FERRE[1];
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Abstract: Striatal GABAergic neurons co-expressing Gs-coupled dopamine D_1 receptors (D_1Rs) and Gi-coupled μ-opioid receptors (MORs) exhibit hypersensitivity in animal models of opioid withdrawal (OW) and restless legs syndrome (RLS). We hypothesized that this hypersensitivity drives the characteristic restlessness of both conditions and depends on altered functional interactions within MOR-D_1R heteromers. Concurrently, MORs that heteromerize with galanin Gal_1 receptors (Gal_1Rs) in the ventral tegmental area have been implicated in the dopaminergic effects and abuse liability of opioids. Notably, the reduced abuse liability of certain MOR agonists, including the methadone enantiomer S-methadone and the novel superagonist analgesic N-desethyl-fluornitrazene (DFNZ), has been linked to an allosteric mechanism dictating a specific loss of efficacy at the MOR-D_1R heteromer. In this study, we evaluated the effects of D_1R and Gal_1R co-expression on the MOR-mediated G protein activation of diverse opioids, including R- and S-methadone, DFNZ, morphine, buprenorphine, fentanyl, DAMGO, and endomorphin-1. A NanoBiT assay was utilized in transfected HEK-293T cells to compare MOR-mediated Go protein coupling in cells expressing MOR alone versus those co-expressing D_1R or Gal_1R. We observed distinct, ligand-specific efficacy (Emax) shifts, with the most remarkable differences occurring for S-methadone, DFNZ, morphine, and buprenorphine. In the presence of Gal_1R, S-methadone showed no response and DFNZ displayed significantly blunted Go protein activation. However, while S-methadone showed a 50% reduced response when co-expressed with D_1R, DFNZ exhibited a significantly increased efficacy of 135%. Remarkably, buprenorphine, which acts as a weak partial agonist at the MOR alone with only 20% of morphine's efficacy, showed a further 60% decrease in efficacy in the presence of Gal_1R but a striking 240% increase in efficacy in the presence of D_1R. The same qualitative results were obtained when measuring adenylyl cyclase signaling (cAMP formation). Computer modeling in silico analysis is being performed to elucidate molecular mechanisms driving the heteromer-dependent differential effects of these opioids. These results strongly support the therapeutic use of buprenorphine for the restlessness associated with RLS and OW, and encourage the clinical application of S-methadone and DFNZ. More generally, this study represents a proof of concept for leveraging the differential allosteric properties of distinct MOR heteromers to develop opioids with enhanced therapeutic profiles and reduced side effects.

Disclosures: G. Enten: None. **N. Llopart:** None. **A. Alonso-Carrasco:** None. **M. Ciruela Jardi:** None. **M. Valle leon:** None. **N. Cai:** None. **C.J. Earley:** None. **S. Moreno:** None. **V. Casadó Anguera:** None. **L. Pardo:** None. **V. Casadó:** None. **S. Ferre:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.16/O8

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural funds of the National Institute on Drug Abuse

Title: Striatal dopamine D_1 receptor function is modulated by μ-opioid receptors through receptor heteromerization

Authors: *W. SANCHEZ[1], A. ALONSO-CARRASCO[2], N. LLOPART[2], M. VALLE LEON[1,3], M. CIRUELA JARDI[4], C. R. QUIROZ[1], N. CAI[1], C. J. EARLEY[3], E. MORENO[2], V. CASADÓ ANGUERA[2], L. PARDO[4], V. CASADÓ[2], S. FERRE[1];
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Abstract: Striatal GABAergic neurons co-expressing the Gs-coupled dopamine D_1 receptor (D_1R) and the Gi-coupled μ-opioid receptor (MOR) exhibit hypersensitivity in animal models of opioid withdrawal and restless legs syndrome (RLS). We hypothesized that this hypersensitivity drives the restlessness characteristic of both conditions and depends on altered functional interactions within MOR–D_1R heteromers. Because prior evidence for functional striatal MOR–D_1R heteromers has been strictly indirect, this study aims to provide definitive *in situ* and *in vivo* evidence of their existence while characterizing their core functional and pharmacological properties. Using bimolecular luminescence complementation in HEK-293T cells and synthetic transmembrane domain (TM) peptides, we identified a heteromeric interface involving TM4 and TM5 of both receptors. In cells co-expressing MOR and D_1R, D_1R agonist (SKF38393)-induced cAMP formation was counteracted by the MOR agonist endomorphin-1 and by the MOR antagonist naloxone. These inhibitory effects were reversed by MOR and D_1R TM4 and TM5 peptides, demonstrating dependence on heteromerization. Furthermore, a NanoBiT assay demonstrated an allosteric mechanism within the heteromer whereby naloxone, but not methadone, counteracted SKF81297-induced Gs protein activation. Proximity ligation assays confirmed the *in situ* presence of MOR–D_1R heteromers in the mouse striatum, which were specifically disrupted by MOR TM4 and TM5 peptides. Finally, *in vivo* fiber photometry using a genetically encoded cAMP biosensor revealed that systemic SKF81297-induced striatal cAMP increases were inhibited by methadone and naloxone. We are leveraging molecular modeling and local TM peptide administration to further resolve the structural mechanics of this naloxone cross-antagonism. Ultimately, our findings identify MOR–D_1R heteromers as a significant receptor population in the striatum and a novel therapeutic target for opioid use disorder and RLS.

Disclosures: W. Sanchez: None. **A. Alonso-Carrasco:** None. **N. Llopart:** None. **M. Valle leon:** None. **M. Ciruela Jardi:** None. **C.R. Quiroz:** None. **N. Cai:** None. **C.J. Earley:** None. **E. Moreno:** None. **V. Casadó Anguera:** None. **L. Pardo:** None. **V. Casadó:** None. **S. Ferre:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.17/P1

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural funds of the National Institute on Drug Abuse

Title: Exploring dopamine D_1-D_3 receptor heteromer function in mice with impaired D_3-dependent G protein signaling

Authors: *C. QUIROZ[1], N. BETARI[2], W. REA[1], M. CIRUELA JARDI[3,4], L. PARDO[3], E. MORENO[4], K. SAHLHOLM[5,2], S. FERRE[1];
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Abstract: The striatal dopamine D_3 receptor (D_3R) forms heteromers with the dopamine D_1 receptor (D_1R), which play a critical role in mouse exploratory locomotion by mediating the locomotor-activating effects D_1R agonists. This behavior correlates with D_1R-mediated β-arrestin recruitment by the D_1R–D_3R heteromer, a process requiring cooperative co-activation of both receptors. *In vitro* evidence suggests this cooperation relies on functional antagonism at the adenylyl cyclase (AC) level: D_3R/Gi signaling counteracts D_1R/Gs-mediated AC activation, shifting D_1R from G-protein-dependent to β-arrestin-dependent signaling. Here, we characterize a novel D_3R mutant (D_3R^{A131W}) that selectively abolishes G-protein signaling while preserving β-arrestin recruitment. When expressed at wild-type levels, D_3R^{A131W} fails to inhibit AC or trigger potassium channel opening. In HEK-293T cells co-expressing D_1R and D_3R^{A131W}, the D_2R-like agonist pramipexole fails to potentiate β-arrestin recruitment induced by the D_1R agonist SKF81297. Crucially, this disruption translates *in vivo*: reserpinized mice expressing D_3R^{A131W} display a significant reduction in pramipexole's ability to potentiate SKF81297-induced locomotion. These results confirm that intact G-protein signaling is necessary for the cooperative effects of D_1R and D_3R agonists on β-arrestin recruitment and behavioral activation. Given the implication of D_1R–D_3R heteromers and downstream β-arrestin pathways in L-DOPA-induced dyskinesia (LID) in Parkinson's disease, we predict that mice expressing the D_3R^{A131W} will exhibit reduced dyskinesia in a rodent model of LID, a hypothesis currently under investigation.

Disclosures: C. Quiroz: None. **N. Betari:** None. **W. Rea:** None. **M. Ciruela Jardi:** None. **L. Pardo:** None. **E. Moreno:** None. **K. Sahlholm:** None. **S. Ferre:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.18/P2

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural funds, National Institute on Drug Abuse

Title: Targeting the dopamine D_1-D_3 receptor heteromer interface with small-molecule drugs

Authors: *W. REA[1], M. CIRUELA JARDI[2], N. CAI[1], C. R. QUIROZ[1], M. CUI[3], C. R. BISHOP[4], L. PARDO[2], E. R. MORENO[5], S. FERRE[1];
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Abstract: Heteromerization of G protein-coupled receptors (GPCRs) determines significant allosteric effects that fundamentally modify receptor pharmacology. The ability to selectively alter this heteromerization using small molecules presents a novel pharmacological opportunity, allowing the separation of monomeric receptor functions from heteromeric allosteric effects. We have previously investigated the cannabinoid CB_1 receptor-serotonin 5-HT_{2A} receptor (CB_1R-5-HT_{2A}R) heteromer, which is implicated in THC-induced cognitive side effects. The interface of the CB_1R-5-HT_{2A}R heteromer is located at transmembrane helices 5 and 6 (TM5-TM6), as confirmed through bimolecular fluorescence complementation (BiFC) assays. Using *in silico* and *in vitro* approaches, we characterized a conserved, shallow hydrophobic pocket designated as orphan site 5 (OS5) within this interface and identified three small-molecule compounds that specifically bind to the 5-HT_{2A}R TM5-TM6 interface. *In vitro* assays demonstrated that these compounds successfully prevented heteromer formation and abolished heteromerization-dependent negative crosstalk without interfering with G protein coupling. After establishing this *in vitro* proof of concept, we expanded this targeted paradigm to the dopamine D_1 receptor-D_3 receptor (D_1R-D_3R) heteromer, which shares the same structural TM5-TM6 interface. The D_1R-D_3R heteromer plays a key role in exploratory locomotion in mice; specifically, it mediates the locomotor-activating effects of D_1R agonists, which correlates with D_1R-mediated β-arrestin recruitment by the D_1R-D_3R complex. This recruitment depends on the cooperative co-activation of both receptors. We identified Compound Z, which binds to the same conserved OS5 pocket in the D_3R. Compound Z successfully altered D_1R-D_3R heteromerization *in vitro* and reduced D_1R agonist-induced β-arrestin recruitment by the heteromer. Furthermore, systemic administration of Compound Z significantly reduced the cooperative locomotor activation induced by D_1R and D_3R agonists in reserpinized mice. These results constitute the first *in vivo* demonstration of using small molecules to therapeutically target and alter the allosteric effects caused by GPCR heteromerization. Given the implied involvement of D_1R-D_3R heteromers in L-DOPA-induced dyskinesia (LID) in Parkinson's disease, we are now evaluating the effects of Compound Z in a rodent model of LID.

Disclosures: W. Rea: None. **N. Cai:** None. **C.R. Quiroz:** None. **M. Cui:** None. **C.R. Bishop:** None. **E.R. Moreno:** None. **S. Ferre:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.19/P3

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural Funds of the National Institute on Drug Abuse

Title: Targeting the dopamine D_1-D_3 receptor heteromer in Restless Legs Syndrome

Authors: *S. FERRE[1], Y.-Y. LAI[2], B. M. KEEGAN[1], M. M. CIRUELA JARDI[3], J.-J. CAO[1], J.-C. HSIEH[4], C. J. EARLEY[5], L. SHI[1], E. MORENO[6], L. PARDO[3], A. H. NEWMAN[1], J. M. SIEGEL[2];
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Abstract: In the striatum, dopamine D_3 receptors (D_3Rs) are localized in dopamine D_1 receptor (D_1R)-expressing GABAergic spiny neurons, where they form D_1R-D_3R heteromers. We demonstrated that these heteromers play a key role in exploratory locomotion in mice. Specifically, they mediate the locomotor-activating effects of D_1R agonists, which correlate with D_1R-mediated β-arrestin recruitment by the D_1R-D_3R complex. This recruitment depends on the cooperative co-activation of both receptors; blocking D_3R activity with selective antagonists, such as PG01042 or PG01037, triggers cross-antagonism that inhibits D_1R-mediated β-arrestin recruitment and subsequently reduces D_1R agonist-induced locomotor activity. Given the implied involvement of D_1R-D_3R heteromers in L-DOPA-induced dyskinesia (LID) in Parkinson's disease, we predicted and demonstrated therapeutic efficacy of both D_3R antagonists in a rodent model of LID. Extending this rationale to restless legs syndrome (RLS), where experimental data suggest increased sensitivity of striatal D_1R spiny neurons, we now evaluated the therapeutic potential of PG01042 and PG01037 in a brain iron-deficient rat model of RLS. Periodic leg movements (PLMs) during sleep and wake and sleep fragmentation were analyzed. In parallel, G-protein activation and β-arrestin-1/2 recruitment were measured via BRET assays in HEK-293T cells expressing either D_3R alone or co-transfected with D_1R. Molecular dynamics simulations were also performed to define the distinct molecular profiles of PG01042 and PG01037. In iron-deficient rats, the two compounds produced opposite behavioral effects: PG01042 dose-dependently reduced motor symptoms and improved sleep quality, whereas PG01037 dose-dependently exacerbated motor symptoms and failed to improve sleep. PG01042 behaved as a D_3R partial agonist for both G-protein activation and β-arrestin recruitment. In contrast, PG01037 acted as a partial agonist for β-arrestin recruitment but exhibited inverse agonism toward G-protein activation. Notably, co-transfection with the D_1R abrogated the partial efficacy of both compounds at β-arrestin recruitment. These functional differences in G-protein activation were attributed to subtle variations in the positioning of the chloro substituents on their respective 2,3-dichlorophenyl moieties. Overall, these findings highlight the therapeutic potential of treating RLS with D_3R ligands that share the distinct pharmacological profile of PG01042. Accordingly, evaluation of cariprazine analogues is currently underway.

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Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.20/P4

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Intramural funds of the National Institute on Drug Abuse
Robert and Sherrie Frankel Postdoctoral Fellowship in RLS Research

Title: Striatal μ-opioid-dopamine D1 receptor heteromers drive dopaminergic hypersensitivity in a rodent model of restless legs syndrome

Authors: *M. VALLE LEON[1,2], G. ENTEN[1], W. REA[1], C. R. QUIROZ[1], W. SANCHEZ[1], S. ALBORNOZ MARIN[3], A. RULE[3], N. CAI[1], F. CIRUELA[4], C. J. EARLEY[2], S. FERRE[1]; [1]Integrative Neurobio. Section, NIH, NIDA IRP, Baltimore, MD; [2]Dept Neurol, Johns Hopkins Sch. Med., Baltimore, MD; [3]Dept. of Envrn. Hlth. and Engin., Johns Hopkins Bloomberg Sch. of Publ. Hlth., Baltimore, MD; [4]Univ. de Barcelona, L'Hospitalet de Llobregat, Spain

Abstract: We previously hypothesized that restless legs syndrome (RLS) and opioid withdrawal share common neurobiological mechanisms. This hypothesis is supported by the efficacy of μ-opioid receptor (MOR) agonists in relieving RLS symptoms and the emergence of an RLS-like phenotype during opioid withdrawal. MORs are predominantly expressed in striatal GABAergic neurons within the striosomal compartment that co-express dopamine D_1 receptors (D_1Rs). These neurons project to ventral midbrain dopaminergic cells and the internal segment of the globus pallidus, equivalent to the entopeduncular nucleus (EPN) in rodents. Because opioid withdrawal in mice is associated with increased sensitivity of striosomal MOR–D_1R neurons, we examined whether a similar hypersensitivity occurs in mice with diet-induced brain iron deficiency (BID), an established RLS model. BID was induced by feeding post-weaning mice a low-iron diet and confirmed by mass spectrometry measurements of striatal iron levels. To evaluate circuit-level effects, fiber photometry was performed following the injection of a viral GABA biosensor into the EPN. GABA release was assessed after systemic administration of the D_1R agonist SKF81297 and the MOR agonist methadone. Locomotor activity was also evaluated in non-reserpinized and catecholamine-depleted reserpinized mice to isolate MOR–D_1R interactions from endogenous dopamine signaling. Striatal mRNA expression of D_1R, MOR, and adenosine A_1 receptor (A_1R), which is a modulator of D_1R signaling typically downregulated in BID, was measured via quantitative RT-PCR. Finally, a NanoBiT assay was used in transfected HEK-293T cells to investigate D_1R-mediated Gs protein coupling and β-arrestin recruitment within the MOR–D_1R heteromer. A minimal locomotor-activating dose of SKF81297 induced significant EPN GABA release in BID mice but not in controls, whereas methadone significantly blunted EPN GABA release in BID mice following either saline or SKF81297 administration. BID was also associated with a significant reduction in both A_1R and MOR mRNA expression. In transfected cells, co-expression of MORs, even in the absence of opioid ligands, impaired the ability of SKF81297 to promote D_1R–Gs coupling, indicating a powerful antagonistic allosteric modulation of D_1R function by MOR within the heteromer. Together, these findings suggest that the downregulation of striatal MORs is a driving factor behind BID-induced dopaminergic

hypersensitivity in striosomal MOR–D_1R neurons, highlighting a potential core pathogenic mechanism in RLS.

Disclosures: M. Valle leon: None. **G. Enten:** None. **W. Rea:** None. **C.R. Quiroz:** None. **W. Sanchez:** None. **S. Albornoz Marin:** None. **A. Rule:** None. **N. Cai:** None. **F. Ciruela:** None. **C.J. Earley:** None. **S. Ferre:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.21/P5

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: T32 MH015330

Title: Beyond up and down: interpreting entropy-like measures in single-channel EEG during psilocybin and N,N-dimethyltryptamine administration

Authors: *N. H. HELLER[1], G. LOFLAND[2], F. S. BARRETT[3];
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Abstract: Entropic quantities (e.g. entropy rate and production) are calculable values that precisely describe how probabilistic systems explore their state space over time. Entropy-related measures (e.g. Lempel-Ziv complexity) are estimators of entropic quantities that are often interpreted through Entropic Brain Theory as evidence that psychedelics increase neural entropy, but this framing leaves three linked questions underspecified: which signal features carry these estimates, whether estimates imply drug-induced increases or decreases in entropic quantities, and whether estimators applied to coarse-grained signal projections preserve latent state-space entropic quantities. To test these, we used single-channel occipital EEG and reduced order models. We focused on entropy rate, which quantifies temporal unpredictability (uncertainty about future states given past states), estimated with Lempel-Ziv complexity, permutation, sample, and multiscale entropy, and entropy production, linked to irreversible probability circulation (time-asymmetry of state-space trajectories), estimated with slope skew, rise-fall magnitude, rise-fall energy, and rise-fall extreme (time-asymmetry measures). We then analyzed psilocybin (PSI) Oz EEG during eyes-closed (EC) and eyes-open (EO) rest (N=34) and N,N-dimethyltryptamine (DMT) O2 EEG during EC rest (N=30), using paired t tests and phase-randomized surrogate nulls that preserve spectral amplitude and linear-Gaussian autocorrelation while disrupting phase-dependent temporal organization. Entropy-rate-like estimates increased in 11/12 drug-by-state measure tests (paired dz=-0.18 to 1.71; p=2.9e-10 to .86), but corresponding surrogate-rank shifts were weak/inconsistent (dz=-0.34 to .72), indicating that much of the effect was carried by preserved spectral/linear structure. Time-asymmetry measures showed robust null-relative shifts (rank dz=-1.17 to -.40; p=5.2e-7 to .027): observed waveform temporal

asymmetry decreased toward the phase-randomized null in PSI and DMT EC, but increased away from it in PSI EO. Finally, FitzHugh-Nagumo simulations showed that projected waveform asymmetry need not faithfully track hidden probability circulation: waveform projections are most time-symmetric when latent probability circulation is strongest. Thus, it is not yet known whether psychedelic effects on entropy-like EEG measures are interpretable as a single up/down entropy axis: it depends on the entropic target, the signal feature carrying the estimator, the brain state, and the observation process mapping hidden dynamics into measured electrophysiological signals (e.g. EEG).

Disclosures: N.H. Heller: None. **G. Lofland:** None. **F.S. Barrett:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.22/P6

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels
Moore Foundation

Title: PsychTag A GPCR State Gated Proximity Labeling Platform for Psychedelic Activated Proteomes

Authors: *H. MALI[1], C. DOUGHERTY[1], C. K. KIM[3,1], C. LEUNG[2];
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Abstract: Neuropsychiatric disorders affect ~2.2% of the global population and are often associated with persistent alterations in neuronal biochemistry. Psychedelic drugs are currently being explored as a potential therapeutic for treating treatment-resistant patient populations. One class of these drugs primarily target the serotonin 5-HT_{2A} receptor (5-HT_{2A}R); yet the diversity of downstream signaling mechanisms at this receptor in neurons remain incompletely understood. One approach to tag and identify proteins recruited to activated receptors include proximity labeling enzymes (BioID/TurboID). However, existing approaches tether these enzymes to the C terminus of receptors, resulting in constitutive protein tagging regardless of receptor activation, making it difficult to identify proteins dynamically recruited to activated GPCRs in response to a drug.To address this, we developed PsychTag, a GPCR-based proximity labeling tool where the large split-TurboID fragment (sTbC) is fused to the C-terminal tail of 5-HT_{2A}R, while the small fragment (sTbN) is tethered to β-arrestin2. Upon 5-HT_{2A}R activation, β-arrestin2 is recruited to the receptor, driving split-TurboID reconstitution and biotinylation of nearby proteins. Agonist alone produces no signal, as endogenous biotin is insufficient for robust labeling. Exogenous biotin alone yields no signal, as both fragments remain separated. PsychTag thus labels proteins only when both a 5-HT_{2A}R agonist and exogenous biotin are simultaneously present, serving as a dual-input gate suppressing constitutive labeling.To design the optimal version of PsychTag, we employed Rosetta RFdiffusion and AlphaFold-Multimer to evaluate

structural rankings, and systematically screened fusion orientations, domain swapping, and P2A co-expression strategies. In HEK293T cells, PsychTag achieves ~2-fold SNR above control ($p<0.001$, n=4), with a 5-HT EC_{50} of 21.8 μM ($R^2=0.98$) and peak SNR of ~2.8-fold at 80 μM exogenous biotin ($R^2=0.97$). AAV-delivered PsychTag in primary rat cortical neurons achieves ~5-fold SNR, validating physiological relevance. In summary, our PsychTag technology enables a GPCR-state-gated proximity labeling platform for live capture of psychedelic-activated proteomes, generalizable to dopamine, opioid, and other neuromodulator systems.

Disclosures: H. Mali: None. **C. Dougherty:** None. **C.K. Kim:** None. **C. Leung:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.23/Q1

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant MH002946-13

Title: Amphetamines induce cholesterol homeostasis pathway genes through a trace amine-associated receptor 1 (TAAR1)-dependent mechanism

Authors: *G. J. GRUMBAR[1,2], W. SUN[1,3], S. G. AMARA[1];
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Abstract: Stimulants such as amphetamines are commonly used therapeutic agents as well as drugs of abuse. Given that amphetamines can activate multiple signaling pathways within dopamine neurons, we wanted to explore potential gene expression changes that occur following administration of amphetamines. Our group examined the gene expression changes resulting from acute and sub-chronic methamphetamine administration and found that that dopamine neurons display a robust enhancement in both nuclear transcripts and actively translated RNAs for cholesterol homeostasis pathway genes. Although amphetamine also caused these increases in gene expression, another commonly prescribed stimulant, methylphenidate, which blocks the dopamine transporter (DAT) but does not enter the cell as amphetamine and methamphetamine do, did not activate these pathways. This suggests that these gene expression changes are not due to blockade of DAT and elevation of extracellular dopamine. Because amphetamines are potent agonists of an intracellular G protein-coupled receptor, the trace amine-associated receptor 1 (TAAR1), we hypothesized that these gene expression changes were downstream of TAAR1. Here, we have replicated the *in vivo* amphetamine- and methamphetamine-induced changes in cholesterol homeostasis pathway gene expression using qPCR in the N27-A dopamine neuron-like immortalized cell line and then examined the potential signaling pathways that might be involved. In the N27-A cell line, both amphetamine and methamphetamine incubation resulted in the induction of the cholesterol homeostasis pathway genes, *Hmgcr* and *Ldlr.* Furthermore, these

changes were dependent on the activation of the sterol regulatory element-binding protein 2 (SREBP2), the main transcription factor regulating cholesterol homeostasis pathway gene expression. The increases in *Hmgcr* and *Ldlr* expression were also dependent on the activation of TAAR1, since they were blocked by the co-application of the TAAR1 antagonist EPPTB. Interestingly, blockade of two known TAAR1 signaling pathways, protein kinase A (PKA) and Rho-associated protein kinase 1/2 (ROCK1/2), did not prevent the methamphetamine-induced increases in *Hmgcr* and *Ldlr* expression. Inhibition of G protein-coupled receptor kinase (GRK) activity to prevent β-arrestin recruitment or inhibition of G protein β/γ subunit signaling also failed to prevent the methamphetamine-induced changes in *Hmgcr* and *Ldlr* expression. These results highlight the diverse actions of amphetamines and indicate that TAAR1 agonists such as amphetamines can modulate the expression of key cholesterol homeostasis pathway genes in dopamine neurons.

Disclosures: G.J. Grumbar: None. **W. Sun:** None. **S.G. Amara:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.24/Q2

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: RS-2026-25471234
RS-2026-25504488
RS-2024-00332875

Title: Presynaptic glutamatergic signaling regulates local translation in distal axons and presynaptic terminals

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Abstract: Local translation enables rapid and dynamic remodeling of the proteome within neuronal processes in response to local demands, independent of protein transport from the soma. Although accumulating evidence supports the presence of active local translation in distal axons, the receptor-mediated mechanisms governing local translation in presynaptic terminals remain poorly understood. Here, we show that a presynaptic glutamate receptor positively regulates local translation in distal axons and presynaptic terminals of rat primary cortical neurons through G protein-, PLC-, and CaMKII-dependent signaling pathways. Using translating ribosome affinity purification followed by sequencing (TRAP-seq), we find that receptor activation enhances the local translation of ribosome-associated transcripts linked to

mitochondrial function within axons. Furthermore, receptor-dependent local translation of mitochondrial proteins is required for axon outgrowth and branching. Together, our findings identify a presynaptic glutamatergic signaling pathway that regulates local translation and reveal a mechanism linking glutamatergic activity to remodeling of the presynaptic proteome.

Disclosures: D. Park: None. **C. Lindsley:** None. **C.M. Niswender:** None. **Y. Suh:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.25/Q3

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: DBT-22-0276

Title: The role of the antagonist in the group I mGluR trafficking and mGluR-mediated AMPA receptor endocytosis

Authors: *S. PAL[1], S. BHATTACHARYYA[2,1];
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Abstract: Glutamate is the most predominant excitatory neurotransmitter in the central nervous system. Glutamate activates two types of receptors in the central nervous system- ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs), which are G protein-coupled receptors (GPCRs). Group I mGluRs are involved in various experience-dependent synaptic plasticity, including learning and memory formation. They have also been implicated in several neuropsychiatric disorders. Trafficking of these receptors controls the accurate spatio-temporal localization and activity of these receptors. Any alterations in the trafficking pathway can lead to severe pathological consequences. Some amount of work has been done in understanding the underlying cellular and molecular mechanisms of agonist-mediated desensitization and internalization of group I mGluRs. Some GPCRs could also undergo internalization by antagonists, but the mechanisms of antagonist mediated trafficking of GPCRs and their physiological significance in the brain have not been studied in detail. This study aims to investigate the cellular and molecular mechanisms of antagonist (MTEP) mediated mGluR5 trafficking. We would also investigate the role of MTEP in the mGluR mediated AMPA receptor endocytosis, which is the cellular correlate for mGluR dependent synaptic plasticity. Using techniques like the dual antibody feeding assay, molecular replacement approach, confocal microscopy, western blotting assay and co-immunoprecipitation assay in the mouse primary hippocampal neurons, we have studied the cellular and molecular mechanisms of the MTEP mediated trafficking of mGluR5. Our data suggest that 100 µM MTEP induces maximum internalization of the mGluR5 at 30 minutes post MTEP treatment via a clathrin and dynamin dependent mechanism. Protein kinase C (PKC) plays a critical role in the MTEP

mediated endocytosis of mGluR5. Mutation of the PKC-phosphorylation residues (S839 and S901) on the mGluR5 disrupts the interaction of PKC with mGluR5 and it inhibits the MTEP mediated endocytosis of the receptor. The MTEP mediated endocytosed receptors recycle back to the cell surface at 60 minutes post MTEP treatment in a protein phosphatase 2A dependent process. Introduction of the phosphomimetic mutations at the PKC phosphorylation residues on the mGluR5 inhibits the recycling of the MTEP mediated endocytosed receptors. Future studies will be concentrated on investigating the role of various post-synaptic density proteins in this MTEP mediated endocytosis of mGluR5. Finally, the role of MTEP in the mGluR mediated AMPA receptor endocytosis will also be studied.

Disclosures: S. Pal: None. **S. Bhattacharyya:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.26/Q4

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
NIH NIMH/FIC/NCCAM grant R21MH095644
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Contract # HHSN-271- 2013-00017-C and HHSN- 271-2018-00023-C (NIMH - PDSP)
Plant material available through the Access Contract for Genetic Resources 003-2019-MINAGRI-SERFOR/DGGSPFFS-DGSPF and its Addendum No 1

Title: Bioactive compounds for histamine HRH1, HRH2, HRH4, MRGPRX2 and NTS1: potential novel modulators of neuropsychiatric conditions associated with mast cell dysfunction

Authors: *C. GALLO[1], G. POLETTI[1], J. ALBAN[2], A. J. VAISBERG[1];
[1]Univ. Peruana Cayetano Heredia, Lima, Peru; [2]Univ. Nacional Mayor de San Marcos, Lima, Peru

Abstract: The role of histamine, MRGPRX2 and neurotensin NTS1 GPCR receptors in mast cell function has been widely recognized. Also, there is increasing evidence that at least some cases of chronic fatigue, cognitive impairment, myalgia, headache or migraine can be associated with dysregulations in the function of mast cells.
Mast cell activation disease (MCAD) has been associated with neuropsychiatric disorders, comprising dysautonomia, neuropathy, myalgia, migraine, headache, cognitive dysfunction, restless legs syndrome, sleep disturbance, non-pulsatile tinnitus, depression, generalized anxiety, and panic attacks.
Previous studies have led us to gather a repository of ethanol extracts from 477 plant collections

corresponding to 265 species from 87 different plant families, that are used in Peruvian traditional medicine for the treatment of CNS disorders.
We have identified that 136 of these extracts show high activity for two or three of either HRH1, HRH2, HRH4, MRGPRX2 or NTS1, through ligand binding (HRH1, HRH2, HRH4) or functional Tango-beta-arrestin assay (MRGPRX2, NTS1) with the collaboration of the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill.
Coincidently, these extracts are used in Peruvian traditional medicine for treating diverse conditions that fall under the scope of MCAD, such as depression, insomnia, “sadness”, “madness”, “heart palpitations”, “nervousness”, “clarifying the mind”, headache, rheumatism, “body aches” among others.
The identified plant extracts would be worth testing not only for potential multi-target therapy and the discovery of novel active compounds but also for helping to better understand the pathologic mechanisms involved in mast cell dysregulation on the nervous system.

Disclosures: C. Gallo: None. **G. Poletti:** None. **J. Alban:** None. **A.J. Vaisberg:** None.

Poster

PSTR256: G-Protein Coupled and Other Receptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR256.27/Q5

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Stanley Medical Research Institute grants 03-484 and 06T-797
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Plant material available through the Access Contract for Genetic Resources 003-2019-MINAGRI-SERFOR/DGGSPFFS-DGSPF and its Addendum No 1

Title: Bioactive compounds for GPCRs linked to Lewy body dementia: a potential drug discovery path from phytopharmaceuticals

Authors: *G. POLETTI[1], C. GALLO[1], J. ALBAN[2], A. J. VAISBERG[1];
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Abstract: Traditional medicine knowledge can lead to the discovery of novel therapeutics for CNS disorders and help to unravel yet poorly understood biological processes behind the occurrence of these diseases. Rescuing traditional medicine practices is one of the possible avenues to identify novel pharmacological approaches for clinical conditions like Lewy body Dementia for which adjuvant pharmacotherapies are strongly needed.

Previous studies have led us to gather a repository of ethanol extracts from 477 plant collections corresponding to 265 species from 87 different plant families, that are used in Peruvian traditional medicine for the treatment of CNS disorders.
Thanks to the support of the NIMH Psychoactive Drug Screening Program (PDSP) - University of North Carolina, Chapel Hill (UNC), we were able to screen these extracts for several G-Protein Coupled Receptors (GPCRs) which have been linked to Lewy body dementia, such as dopamine DRD1, DRD2, cholinergic muscarinic CHRM1, CHRM3, metabotropic glutamate mGluR5, mGluR2/3 (through ligand binding) and the chemokine receptor CXCR4 (through functional Tango-beta arrestin assay).
We have identified 134 plant extracts having at least 4 combined activities to these GPCRs. Noteworthy, these plant extracts are used in Peruvian traditional medicine for treating diverse traits that feature Lewy Body dementia, such as depression, insomnia, “sadness”, “madness”, “nervousness”, “clarifying the mind”, “memory/forgetting” among others.
Our preliminary results point out the importance of ancient medical knowledge as a pathway for drug discovery and remark the worthiness of isolating and identifying the active principles, not only for a potential multi-target therapy for Lewy body dementia, but to advance in the understanding of the pathologic mechanisms involved in its triggering and progression.

Disclosures: G. Poletti: None. **C. Gallo:** None. **J. Alban:** None. **A.J. Vaisberg:** None.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.01/Q6

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

Support: NIH DP2MH136494
AFOSR FA9550-22-1-0078
AFOSR FA9550-23-1-0701
NSF 2120200

Title: Layer 5B dendrites multiplex value, action, and prediction during active sensory learning

Authors: *S. XIAO[1], S. WU[3], R. P. RAO[4], K. JAYANT[2];
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Abstract: Sensory discrimination requires cortical circuits to transform sensory inputs into reliable perceptual decisions, yet how distinct output pathways contribute to this transformation remains unknown. Layer 5B (L5B) thick-tufted pyramidal neurons are uniquely positioned to integrate bottom-up sensory drive onto basal dendrites with top-down predictions onto apical tufts, making them candidate substrates for predictive computation. However, whether different

L5B projection classes, defined by their long-range targets, implement functionally distinct computations during perceptual learning remains unexamined. Here, using two-photon calcium imaging of apical tuft and trunk compartments in projection-class-identified L5B neurons across learning of a two-whisker active touch discrimination task, we reveal a dissociation among three major output streams. Posterior medial thalamus (POm)-projecting L5B neurons show increasing tuft-trunk coupling from naïve to intermediate performance, followed by a reduction at expert-level proficiency, consistent with an actor-critic architecture in which early learning amplifies reward prediction-error signals that are suppressed once behavior is optimized. Superior colliculus (SC)-projecting neurons exhibit monotonically increasing coupling alongside the progressive emergence of trial-locked spatiotemporal population structure, as revealed by Slice Tensor Component Analysis (Slice TCA), implicating this pathway in the continuous updating of an action policy for the task. Pontine (PONS)-projecting neurons, by contrast, show neither coupling changes nor trial-locked dynamics, but display strong time-locked activity consistent with a circuit mechanism that conveys sensory prediction error to PONs for cerebellar learning. Interpreted and recapitulated within an Active Predictive Coding (APC) framework, these results suggest that L5B functions not as a uniform output layer but as a multiplexed predictive engine, parcellating actor-critic valuation, motor update signaling, and forward model computation across anatomically distinct projection classes. These findings establish a circuit-level substrate for hierarchical predictive coding during active sensory perception.

Disclosures: S. Xiao: None. **S. Wu:** None. **R.P. Rao:** None. **K. Jayant:** None.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.02/R1

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

Support: NIH Grant T32GM112596-09
University of Washington Royalty Research Fund Grant GR032157
NIH R01 GM151556
NIH R01 GM144377
NIH R01 NS044163

Title: Dendritic NMDA-dependent amplification of delta-wave oscillations in an experimentally constrained simplified neocortical network model

Authors: *M. Z. NG[1], A. Z. WASILCZUK[2], J. M. CICHON[3], A. PROEKT[2], N. C. DEMBROW[1,4], W. J. SPAIN[1,4];
[1]Neurobio. & Biophysics, Univ. of Washington, Seattle, WA; [2]Anesthesiol. and Critical Care, [3]Anesthesiol. & Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [4]Neurol., Veteran's Admin. Puget Sound Healthcare Syst., Seattle, WA

Abstract: Prominent delta frequency (0.5-3.0 Hz) network oscillations occur in the neocortex under anesthesia, slow wave sleep, and at the onset of some generalized seizures. The mechanisms that underlie this network state remain poorly defined, although we have recently shown that a subset of prefrontal layer 5 extratelencephalic pyramidal (ET) neurons promote both delta oscillations and non-REM sleep in rodents. Here, we asked whether input-rate dependent NMDA-spiking in ET basal dendrites could explain how these neurons promote and amplify slow network oscillations. To do this, we generated simulations in MATLAB of a randomly connected circuit of several hundred excitatory ETs and inhibitory interneurons (3% unidirectional chance of connection). Individual neurons were modeled as leaky integrate and fire neurons with post-spike conductances. To include excitatory input onto ET dendrites, we additionally modeled four distinct compartments, each representing a separate basal dendrite. We used previously collected data from acute mouse brain slices, in which 2P-glutamate uncaging onto ET dendrites provided the voltage responses used in the model ET neurons. The neurons within the circuit also received uncorrelated external input from two sources which were adjusted to maintain similar individual neuron mean firing rates under different conditions. One source was noisy somatic current with an adjustable DC offset to mimic balanced excitatory and inhibitory synaptic current. For the other source, each of the 4 basal dendrites received 10 uncorrelated Poisson-distributed excitatory synaptic inputs with adjustable mean rates. Simulations were run at mean firing rates of ~10 Hz for ET neurons, and ~20 Hz for inhibitory neurons. This was maintained by adjusting the mean Poisson rate of the external dendritic inputs alone (no current) or dendritic inputs with noisy current inputs. The inclusion of experimentally determined dendritic nonlinearities in ET neurons promoted stable delta oscillations in the circuit under both stimulation regimes quantified by power spectral density of ET neuron network activity (peak power at ~1.7). When the dendrites were linearized (i.e. no NMDA-spiking) the dominant network frequency shifted to ET neuron mean firing rate (~10 Hz). Combined, these results suggest that a network with dendritic nonlinearities can transform and amplify uncorrelated inputs from other brain regions into slow network oscillations.

Disclosures: M.Z. Ng: None. **A.Z. Wasilczuk:** None. **J.M. Cichon:** None. **A. Proekt:** None. **N.C. Dembrow:** None. **W.J. Spain:** None.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.03/R2

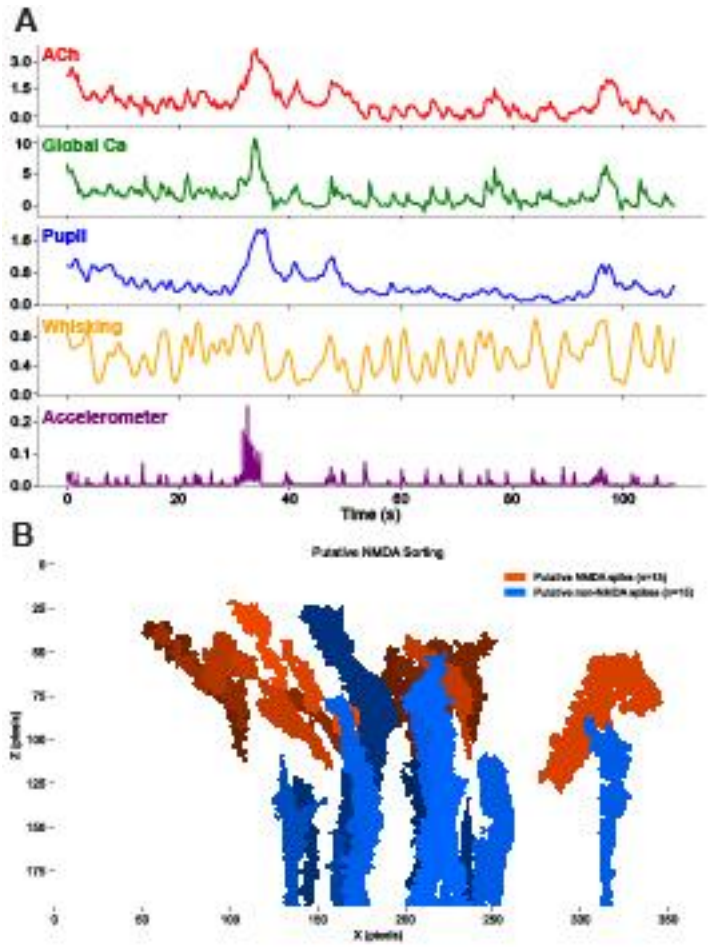
Topic: B.06. Intrinsic Membrane Properties and Signal integration

Support: NIH Grant U19NS123717
BSF Grant 2023104

Title: Behavioral-State-Dependent Calcium Dynamics in the Apical Dendrites of the L5 Pyramidal Cells

Authors: *D. BOGATOVA[1], B. RAUSCHER[2], K. HERREMA[2], Z. YAQOOB[2], J. GIBLIN[2], J. JIANG[3], N. FOMIN-THUNEMANN[2], K. KILIÇ[4], N. CHAI[2], D. BALOG[2], S. RAMIREZ[2], A. CHEN[2], D. A. BOAS[2], E. M. HILLMAN[5], M. LONDON[6], M. THUNEMANN[2], A. DEVOR[2]; [1]Biol., [2]Biomed. Engin., [3]Boston Univ., Boston, MA; [4]Massachusetts Gen. Hosp., Boston, MA; [5]Columbia Univ., New York, NY; [6]Edmond and Lily Safra Ctr. for Brain Sci. and Life Sci. Inst., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Apical dendrites of layer 5 pyramidal cells (L5PCs) are critical integrative hubs in cortical circuits. Their activity patterns, including Ca^{2+} and NMDA spikes, vary across brain states. However, the relationship between neuromodulatory activity and dendritic Ca^{2+}/NMDA spike properties remains unclear. We performed volumetric imaging to characterize spontaneous Ca^{2+} dynamics in apical dendrites of L5PCs in awake, head-fixed mice. We used Rbp4-Cre mice, retro-orbitally injected with PHP.eB AAVs to express GCaMP6s in L5PCs, and a red fluorescent acetylcholine (ACh) sensor GRAB-ACh. Using light sheet microscopy (SCAPE-2.0, Voleti et al. 2019), we imaged spontaneous Ca^{2+} and ACh activity in primary somatosensory (SI) cortex at 5 Hz with a 400 × 200 × 150 μm^3field of view, capturing the top ~150 μm of cortex containing L5PC apical tufts. Simultaneously, we acquired behavior readouts: pupil diameter, whisking, and accelerometer-based movement. Data were analyzed using a custom Python toolbox for detection and segmentation of dendritic events from volumetric time series (**Fig. 1A**). Our results show high correlation between global (volume-averaged) dendritic Ca^{2+} dynamics, ACh, and behavior readouts (Fig. 1). Activity-dependent segmentation of dendritic regions of interest (ROIs) revealed several event types, including vertically oriented putative Ca^{2+} spikes engulfing the nexus and apical trunk, as well as Ca^{2+} transients localized to specific branches (putative NMDA-dependent synaptic events)(**Fig. 1B**). The probability of putative Ca^{2+} spikes increased with ACh. To investigate the relationship between dendritic Ca^{2+} activity and somatic spiking, we used random-access 2-photon microscopy (Femto3D Atlas, Femtonics). Our preliminary data suggest that most events observable within the top ~150 μm correspond to synaptic inputs and dendritic Ca^{2+} spikes rather than back-propagated action potentials. Mechanistic experiments are underway to determine the role of ACh and NMDA-dependent synaptic activity in generation of different dendritic Ca^{2+} events.



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Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.04/R3

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

Support: Brown Subaward 00002443 / NIH Grant
NIH/NINDS 1RF1NS126043-01

Title: In vivo voltage imaging across the full dendritic tree of layer 5 pyramidal neurons

Authors: *Y. WANG, B. LEE, X. WU, J. XU, A. E. COHEN;
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Abstract: Layer 5 (L5) pyramidal neurons are the primary output cells of the cortex, with elaborate dendritic arbors spanning all cortical layers, from basal dendrites in layers 5/6 to distal apical tufts in layer 1. Yet the interplay of dendritic and somatic voltages in behaving animals remains poorly understood. We used high-speed imaging through chronically implanted microprisms to map voltage dynamics across the full arbor of L5 pyramidal neurons in behaving mice.We found that L5 pyramidal neurons exhibit dynamic spike modes, including simple spikes, bursts, and complex spikes accompanied by slower plateau-like apical dendritic depolarizations. Despite their intricate morphology and diverse voltage events, dendritic membrane-potential dynamics were largely captured by two compartments: peri-somatic and apical. Fast dendritic spikes primarily arose from back-propagating action potentials (bAPs). Dendritic subthreshold depolarizations enhanced the efficacy of local bAP transmission. When bAPs arrived in the distal dendrites in conjunction with local depolarization, they triggered dendritic plateau potentials, which in turn drove burst spiking or complex spikes at the soma.Our results describe the membrane potential dynamics of L5 pyramidal neurons across the full dendritic tree in vivo and suggest that dendritic nonlinearities primarily mediate plasticity and bursting in L5 pyramidal neurons.

Disclosures: Y. Wang: None. **B. Lee:** None. **X. Wu:** None. **J. Xu:** None. **A.E. Cohen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Luminos LLC. F. Consulting Fees (e.g., advisory boards); Quiver Biosciences, Exin Therapeutics.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.05/R4

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

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Title: Brain-wide dendritic signals exhibit circuit-specific behavioural modulation

Authors: *S. PERRENOUD[1], P. LAU[2], G. MASTROBERARDINO[1], Z. WANG[1], I. BRAIN LAB[1], L. F. ROSSI[3], K. D. HARRIS[1], B. A. CLARK[1], A. ROTH[1], M. HAUSSER[4,1];
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Abstract: Dendritic signals, particularly backpropagating action potentials (bAPs) that convey information about neuronal output to dendritic synapses, are thought to play key roles in synaptic integration and plasticity. However, how these signals are engaged during behaviour across neuronal populations and brain circuits remains largely unknown. We developed a deep-learning framework to identify extracellular signatures of bAPs in large-scale Neuropixels recordings and applied it to brain-wide data from 139 mice performing a visual decision-making task. We identified robust spatiotemporal signatures of dendritic backpropagation across 72 brain regions spanning cortical and subcortical circuits. These signals were observed throughout frontal, visual, motor, and somatosensory cortices, as well as striatum, midbrain, and medulla, revealing bAPs as a widespread feature of neuronal activity across the brain. At the single-spike level, bAPs depended on recent spike timing and firing history, indicating that dendritic excitability is dynamically regulated on rapid timescales. Task engagement further shaped bAP dynamics, with movement producing broadly distributed effects whereas arousal-related modulation was more region-specific and heterogeneous. During decision-making, sensory and outcome signals were reflected in structured bAP modulation not explained by firing-rate changes alone, with temporal encoding signatures distinct from somatic activity. Moreover, latent behavioural state and decision uncertainty differentially organised bAP and spike-based representations across neural populations. Together, these findings highlight bAPs as brain-wide features of dendritic excitability that are flexibly modulated during sensory processing and behaviour. More broadly, they suggest a previously under-appreciated dimension of population activity through which dendritic signals may contribute to behaviourally relevant computations in biological neural circuits.

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Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.06/R5

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

Support: NIH grants 1R01NS133755
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Title: Fast dendritic excitations primarily mediate back-propagation in CA1 pyramidal neurons during behavior

Authors: *B. LEE[1], P. PARK[2], X. WU[3], D. WONG-CAMPOS[4], J. XU[5], Y. QI[3], Y.-C. HUANG[1], D. G. ITKIS[3], L. LAVIS[6], A. E. COHEN[3];
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Abstract: Dendrites integrate synaptic inputs to trigger action potentials, and dendrites carry back-propagating action potentials (bAPs) to synapses where these signals contribute to plasticity. Despite strong evidence for a rich repertoire of nonlinear dendritic excitations, the *in vivo* roles of these excitations in dendritic integration and back-propagation remain uncertain. Here, we used high-speed voltage imaging through a chronically implanted microprism to map membrane potential dynamics from basal to apical dendrites of CA1 neurons in mice navigating in a virtual reality environment. Despite complex dendritic branch morphology, the dynamics were largely captured by 2 or 3 electrical compartments: basal, soma, and apical. Fast dendritic spikes almost always started from bAPs, indicating that dendritic spikes are primarily a consequence rather than a cause of somatic spiking. These fast spikes sometimes triggered slower apical dendritic plateau depolarizations, which drove complex spikes at the soma. We found that the biophysics of dendritic excitability determined the distribution of simple and complex spikes across a place field. Our results show how CA1 pyramidal neurons convert synaptic inputs to spiking outputs and suggest a primary role of dendritic nonlinearities in mediating activity-dependent plasticity.

Disclosures: B. Lee: None. **P. Park:** None. **X. Wu:** None. **D. Wong-Campos:** None. **J. Xu:** None. **Y. Qi:** None. **Y. Huang:** None. **D.G. Itkis:** None. **L. Lavis:** None. **A.E. Cohen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Luminos LLC. F. Consulting Fees (e.g., advisory boards); Exin Therapeutics, Quiver Biosciences.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.07/R6

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

Support: 5RM1NS132981

Title: Dissecting the Baz1a Pyramidal Neuron Microcircuit

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Abstract: Layer 2/3 (L2/3) pyramidal neurons are a hub in the visual processing stream and recent studies have described cells with molecularly defined, functional subtypes. One cell type found to be active in visual perception are the baz1a L2/3 pyramidal cell. Here, we use a combination of optical methods and patch clamp electrophysiology to investigate the internal physiology of these cells, their dendrites, and their excitatory and inhibitory inputs. Based on our recordings, we were able to classify these cells into burst firing and regular firing baz1a pyramidal neurons as well as a likely inhibitory fast spiking population. Regular firing cells summate better for L2/3 inputs while burst firing cells show higher summation of L5 inputs. Combining L2/3 and L5 input to test integrative functions does not yield significant supralinear output. We report decayed electrical impedance in the dendrites of these cells as a whole and greater in burst firing cells. We further find that L2/3 baz1a dendrites receive a high degree of cortical layer 1 inhibition. These methods and these results may be used in the future to better understand and dissect cortical microcircuits, serving as a roadmap for better understanding of visual processing.

Disclosures: M. Stoessel: None. **J. Basu:** None.

Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

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Program #/Poster #: PSTR257.08/S1

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

Support: the USA National Institute of Neurology and Stroke award (NS138991-01)
the Connecticut IBACS Grant to KDM 402356
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Title: Imaging Dendritic Voltage Signals in Striatal Medium Spiny Neurons

Authors: *K. D. MILICEVIC[1], W. W. LYTTON[2], S. D. ANTIC[3];
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Abstract: Striatal medium spiny neurons (SPNs) of the direct (dSPN) and indirect (iSPN) pathways constitute the major projection neurons of the basal ganglia and receive cortical and thalamic input. Their intrinsic membrane properties and dendritic integration play fundamental roles in striatal information processing. Computational studies of striatal networks frequently represent SPNs as point neurons, omitting important features of dendritic signal processing. Experimental measurements of dendritic voltage dynamics in SPNs remain scarce because conventional electrophysiological techniques provide limited access to distal dendritic compartments. Although computational models of dSPNs and iSPNs have generated important predictions regarding dendritic responses to synaptic input and action potential (AP) backpropagation, these predictions require direct experimental validation. Here, we extend the

experimental characterization of dendritic electrical signaling in SPNs using ex vivo acute brain slices. dSPNs identified by green fluorescent protein expression following crossing of D1-Cre and GFP-LoxP mouse lines were loaded through a patch pipette with a red styryl voltage-sensitive dye (VSD). Voltage imaging revealed robust backpropagation of somatic APs into distal and terminal dendritic segments. In many dendritic branches, APs propagated to terminal dendritic regions with little attenuation or waveform distortion, unlike the filtering expected from purely passive dendritic propagation. Previous studies reported that backpropagation-associated Ca2+ transients decline to near zero at distances of approximately 100 μm from the soma. In contrast, our calcium imaging experiments detected AP-evoked Ca2+ transients throughout the dendritic arbor, including terminal segments located approximately 200 μm from the cell body, providing independent support for the VSD measurements. Both voltage and calcium imaging were performed in multiple dendritic branches from individual SPNs, increasing the robustness and generalizability of the findings. Pharmacological blockade of A-type K^+ channels with 4-aminopyridine significantly enhanced dendritic Ca2+ signals, indicating that local voltage-gated K^+ conductances exert strong control over dendritic excitability. Collectively, the voltage and calcium imaging data demonstrate the presence of active electrical signaling in distal SPN dendritic branches during AP firing. These findings provide experimental constraints on dendritic integration in SPNs and establish an empirical foundation for the refinement and validation of future computational models of striatal function.

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Poster

PSTR257: Somatic and Dendritic Integration

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Program #/Poster #: PSTR257.09/S2

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

Support: NIH Grant 1ZIANS003135-12

Title: Dendritic Integration in Basal Forebrain Cholinergic Neurons

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Abstract: Basal forebrain cholinergic neurons (BFCNs) mediate attention, memory and executive function and their selective degeneration contributes to cognitive deficits in Alzheimer's and Parkinson's diseases. To generate action potential firing patterns, BFCNs integrate synaptic inputs from many brain regions at their dendrites. This dendritic integration is likely to be altered in neurodegenerative disease by the early loss of brainstem and midbrain neuromodulator input. Investigating the features of integration in these cells is therefore critical to advancing our understanding of cognition-relevant cholinergic system physiology and its

changes in neurodegenerative disease. To identify the general features of BFCN integration and the specific contributions of voltage-gated ion channels and neurotransmitter receptors, we perform whole-cell patch clamp recordings of BFCNs in acute brain slices. We electrically evoke synaptic potentials and measure their summation and use pharmacology to identify mediators of non-linear summation. We also measure the biophysical parameters of voltage-gated ion channel currents that may contribute to integration with voltage-clamp recordings. In preliminary experiments, we identified a persistent, non-inactivating voltage-gated sodium current (I_{NaP}) with a peak amplitude of 91.4 ± 6.9 picoamps (pA) that activates 14.2 ± 1.4 millivolts (mV) below action potential threshold. This finding implies I_{NaP} may amplify sub-threshold excitatory synaptic potentials in BFCNs and may promote supra-linear integration. Our ongoing experiments aim to test these hypotheses and identify supra- or sub-linear integration in these neurons. This study provides new insights into the fundamental physiology of basal forebrain cholinergic neurons that underlie cognition and that are disrupted in neurodegenerative diseases.

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Poster

PSTR257: Somatic and Dendritic Integration

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

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Title: Active dendritic electrogenesis in human PVALB interneurons

Authors: *G. JENEI[1], A. DOUIDA[1], E. BAKOS[1], Á. TISZLAVICZ[1], K. PÉLI[1,3], L. NOVAK[5], G. HUTÓCZKI[5], B. BENDE[2], G. TAMAS[4], G. MOLNAR[4], D. WELTER[6], O. IEVGLEVSKYI[1,7], M. GIUGLIANO[7,8,9], V. SZEGEDI[1,3], K. P. LAMSA[1,3];
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Abstract: Human cortical interneurons exhibit substantially longer dendrites than their rodent counterparts, posing a challenge for efficient electrical signal propagation. In elongated human dendrites, excitatory postsynaptic potentials are expected to undergo pronounced attenuation during passive propagation toward the soma. Here, we investigated layer 2/3 parvalbumin-expressing (PVALB) interneurons in acute slices obtained from human neocortical neurosurgical resections. We show that human interneurons enhance dendritic signal propagation through T-type calcium channels. PVALB-immunopositive neurons were examined using whole-cell patch-clamp electrophysiology, pharmacology, single-cell patch-sequencing, immunofluorescent confocal microscopy, two-photon calcium imaging, and single neuron computational modelling. Extracellular stimulation in layers 1 and 5 was used to probe dendritic integration properties. Whole-cell recordings from human PVALB interneurons revealed a subthreshold voltage-dependent depolarizing “hump” near rheobase, a feature absent in rodent fast-spiking cells. This response was blocked by the T-type calcium channel antagonist TTA-P2. Patch-seq analysis showed elevated expression of the CaV3.1 channel subunit (CACNA1G) in human PVALB interneurons, and double-immunohistochemical staining demonstrated CaV3.1 localization in the dendrites. Two-photon calcium imaging further revealed branch-specific dendritic Ca2+ signals that were also blocked by TTA-P2. Our experiments in human and mouse PVALB neurons, combined with a computational model, show dendritic T-type calcium signaling as a species-specific mechanism in PVALB interneurons, to support signal propagation in elongated human neocortical dendrites.

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Poster

PSTR257: Somatic and Dendritic Integration

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR257.11/S4

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

Title: Proteomic characterization of synapses in the human cerebellum and their dysregulation in mental illness

Authors: *M. E. CORTES-GUTIERREZ[1], L. G. RODRIGUEZ[2], R. O'HARA-PAYNE[5], X. FAN[3], N. AYITHAN[3], R. JOHNSON[1], R. SCHWARCZ[6], P. NEMES[4], S. A. AMENT[7]; [1]Univ. of Maryland, Baltimore, MD; [2]Univ. of Maryland, College Park, MD; [3]Univ. of Maryland, BALTIMORE, MD; [4]Dept. of Chem. and Biochem., Univ. of Maryland, College Park, MD; [5]Program in Epidemiology and Human Genet., Univ. of Maryland Sch. of Med., Baltimore, MD; [6]Psychiatry, Maryland Psychiatric Res. Ctr., Baltimore, MD; [7]Dept. of Psychiatry and Inst. for Genome Sci., U Maryland Sch. of Med., Baltimore, MD

Abstract: Changes in the structural components of synapses are thought to contribute to the onset and progression of psychiatric disorders. However, few studies have directly measured the composition of synapses in the human brain. Here, using liquid chromatography mass spectrometry, we conducted discovery proteomic analysis to profile the proteomic composition of synapses on Purkinje cells in the human cerebellar vermis. We identified over 700 proteins, among which we found hallmarks proteins of synaptosomes. We integrated these data with single-nuclei RNA sequencing (snRNA-seq) of schizophrenia and bipolar disorder cases and controls (n=52) to characterize patterns of synaptic dysregulation. Differential gene expression analysis revealed that many of the most significantly altered genes belonged to synapse-associated networks expressed in Purkinje cells, granule cells, and Bergmann glia. In the cerebellum, these three cell types form the tripartite synapses between parallel fibers and Purkinje cells, which represent the most abundant synaptic contacts within the molecular layer. Our findings indicate coordinated dysregulation of cell-surface molecules involved in synaptic organization, including the cell adhesion molecule ROBO2, across both neuronal and glial components of these synapses.

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Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.01/S5

Topic: B.08. Epilepsy

Support: Czech Science Foundation (24-10026S)
ExRegMed (CZ.02.01.01/00/22_008/0004562, MEYS CR)

Title: K2060, a Novel MK-801-Derived NMDA Receptor Channel Blocker, Prevents Audiogenic Seizures in GluN2A-N615S Mice

Authors: *M. HORAK[1], M. LADISLAV[2], M. KOLCHEVA[3], J. NETOLICKY[4];
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Abstract: N-Methyl-D-aspartate receptors (NMDARs) are glutamate-gated ion channels essential for synaptic transmission, neuronal plasticity, and cognitive function. Disrupted NMDAR signaling has been implicated in a wide range of neurodevelopmental and neuropsychiatric disorders. Several pathogenic *de novo* variants occur within the receptor pore, particularly in the M2 re-entrant loop that regulates ion permeation and voltage-dependent Mg^{2+}

block. One such variant, GluN2A-N615S, reduces Mg^{2+} sensitivity and causes NMDAR gain-of-function. A corresponding knock-in (KI) mouse model recapitulates key aspects of the disease phenotype. We investigated the in vivo efficacy of NMDAR channel blockers in GluN2A-N615S KI mice, focusing on K2060, a novel MK-801-derived compound, and compared its effects with memantine. Male WT and N615S KI mice received intraperitoneal injections of vehicle or test compounds and underwent behavioral testing 30 min later. Sensorimotor gating was assessed using acoustic startle response (ASR) and prepulse inhibition (PPI), while anticonvulsant activity was evaluated in an audiogenic seizure (AGS) paradigm. Potential locomotor side effects of K2060 were examined in the open-field test using escalating doses. N615S KI mice exhibited markedly reduced ASR amplitudes compared with WT controls and impaired PPI at higher prepulse intensities. Neither memantine nor K2060 (5 mg/kg) significantly affected ASR or PPI in either genotype. In contrast, all three compounds reduced seizure susceptibility in the AGS model at 5 mg/kg. At the lower dose of 1 mg/kg, however, only K2060 maintained significant anticonvulsant efficacy relative to vehicle-treated controls. Open-field testing revealed no locomotor impairment in WT mice at doses up to 30 mg/kg K2060, whereas N615S KI mice showed reduced locomotion and increased stereotypic behavior at 15 mg/kg. These findings demonstrate superior in vivo potency of K2060 compared with memantine in the GluN2A-N615S model of NMDAR pore dysfunction. Importantly, anticonvulsant efficacy was achieved without disrupting startle reactivity or sensorimotor gating at therapeutically effective doses. Together, the results support K2060 as a promising and well-tolerated pharmacological tool for the treatment and investigation of NMDAR channelopathies caused by pore-region variants. **Funding:** Czech Science Foundation (24-10026S) and ExRegMed (CZ.02.01.01/00/22_008/0004562, MEYS CR).

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Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.02/S6

Topic: B.08. Epilepsy

Support: Italian National Recovery and Resilience Plan (NRRP), M4C2, funded by the European Union – NextGenerationEU (Project IR0000011, CUP B51E22000150006, "EBRAINS-Italy"
EU HORIZON-INFRA-2022-SERV-B-01, project 101147319 — EBRAINS 2.0
Project PRIN 2022ZY5RXB_002 ‘HIPPOCOMP’

Title: The accumulation of extracellular K+ as in vivo model of epilepsy in CA1 pyramidal neurons

Authors: *V. CARPENTIERI[1], C. BERNARD[2], M. MIGLIORE[1];
[1]Natl. Res. Council, Inst. of Biophysics, Palermo, Italy; [2]INSERM U1106, Marseille cedex 05, France

Abstract: Epilepsy is a chronic neurological disorder characterized by recurrent seizures caused by abnormal brain electrical activity. Experimental models often rely on channel mutations, drugs, or direct stimulation. However, these approaches may not fully reproduce in vivo conditions, where seizures can emerge from otherwise normal neuronal activity. Identifying intrinsic seizure mechanisms is therefore essential. A plausible mechanism involves altered extracellular K^+ homeostasis, which maintains electrochemical gradients. Impaired K^+ regulation can cause sustained depolarization, increased excitability and higher seizure susceptibility. To investigate this, we developed a realistic computational model of hippocampal CA1 pyramidal neurons in NEURON, testing whether local dendritic accumulation of extracellular K^+, driven by physiological synaptic inputs, can generate seizure-like activity. Seizure-like events were defined as sudden action-potential bursts associated with a prolonged depolarizing envelope, potentially bringing the neuron close to the depolarization block. Although these events depend on network activity, they can be reproduced at the single-cell level using realistic synaptic input patterns recorded in vivo. In the model, synaptic inputs were distributed across dendrites and activated by spike trains recorded during normal behavior. Extra- and intracellular K^+ dynamics were described by time constants for extrusion, reuptake, diffusion, and astrocytic activity. Under control conditions, neurons showed regular firing with occasional short bursts, while K^+ concentrations remained near physiological values. Even strong synaptic input did not induce somatic seizure-like activity. Conversely, when K^+ reuptake and diffusion were slowed, transient seizure-like events emerged, lasted a few seconds, and were associated with extracellular K^+ increases. These events usually originated in localized dendritic regions and rapidly propagated to the soma. Parameter-space exploration showed that seizure-like activity appears only when K^+ clearance is substantially slowed, confirming the robustness of K^+ homeostasis under normal conditions. Event probability and features depended on synaptic strength, dendritic location, and affected-region size, with basal dendrites prone to pathological initiation. Finally, the model predicts that modulation of specific ionic currents, such as IA, can suppress seizure-like activity even under impaired K^+ dynamics. These findings suggest that altered extracellular K^+ regulation alone may trigger seizures during normal activity and may help identify therapeutic targets.

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Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

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Program #/Poster #: PSTR258.03/S7

Topic: B.08. Epilepsy

Support: NIH 204000-520-101226

Title: Mechanisms of YWHAG-Associated Developmental and Epileptic Encephalopathy in Human iPSC-Derived Cortical Neuronal Models

Authors: *V. VILMONT, R. S. NOWAKOWSKI, Y. ZHOU;
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Abstract: Developmental and Epileptic Encephalopathies (DEEs) are severe neurodevelopmental disorders characterized by early-onset seizures, epilepsy, and persistent cognitive impairment. Pathogenic variants in *YWHAG*, which encodes the 14-3-3γ protein, have been identified as a cause of DEE56; however, the cellular mechanisms by which these variants disrupt human neuronal development and function remain poorly understood. To address this question, we are investigating the effects of the *YWHAG* p.Arg132Cys (R132C) variant using isogenic human induced pluripotent stem cell (iPSC) lines carrying either the mutant (MT) or wild-type (WT) allele. To model human neuronal development, iPSCs will be differentiated into neurons using two complementary approaches: (1) embryoid body (EB)-based neural induction through dual-SMAD inhibition and (2) rapid neuronal conversion via Neurogenin-2 (NGN2) overexpression through lentiviral transduction. Neuronal morphology and maturation will be assessed using immunocytochemistry and Sholl analysis, while neuronal function will be evaluated by whole-cell patch-clamp electrophysiology to characterize intrinsic excitability and synaptic properties. Previous studies from our laboratory using a 14-3-3 functional knockout (FKO) mouse model demonstrated reduced dendritic complexity and spine density in forebrain excitatory neurons, as well as reduced dendritic complexity and increased action potential firing in hippocampal CA1 neurons. Together, these findings indicate that 14-3-3 proteins are critical regulators of neuronal morphology and excitability. Building upon this work, the present study focuses on the specific contribution of the 14-3-3γ isoform encoded by *YWHAG*. We hypothesize that the R132C variant disrupts neuronal maturation, dendritic architecture, and electrophysiological properties relative to the WT controls. These studies will provide important insights into the cellular consequences of pathogenic *YWHAG* variants and may reveal mechanisms underlying neurodevelopmental dysfunction and epilepsy in DEE56.

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Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.04/S8

Topic: B.08. Epilepsy

Support: NIH R01NS120945

Title: Lactate as a neuromodulator

Authors: *D. GYAMFI[1], H. SUN[1], J. KAPUR[2];
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Abstract: During seizures, excessive neuronal firing drives glycolytic activity and rapid lactate accumulation in affected brain regions. Lactate has emerged as a neuromodulator acting through hydroxycarboxylic acid receptor type 1 (HCAR1), a Gi/o-coupled GPCR broadly expressed throughout the hippocampus. HCAR1 signaling is complex: it engages both Gαi/o and Gβγ pathways, and its effects on neuronal excitability are highly cell-type dependent. Whether HCAR1 exerts an excitatory or inhibitory effect in the dentate gyrus has not been established. The dentate gyrus serves as a critical gate filtering excitatory input into the hippocampal circuit. We therefore investigated whether lactate-HCAR1 signaling alters DGC excitability.Using GCaMP7-based calcium imaging in acute hippocampal slices, we find that lactate significantly increases calcium activity in DGCs. This effect is mimicked by the selective HCAR1 agonist 3-chloro-5-hydroxybenzoic acid (3Cl-HBA) and fully abolished by the NMDAR antagonist DL-AP5, demonstrating that HCAR1 drives DGC excitability through an NMDAR-dependent mechanism. This effect is blunted in HCAR1-KO mice. Consistent with a PKC-mediated pathway downstream of Gβγ, PKC inhibition blocks this effect. Whole-cell patch-clamp recordings confirm that lactate increases spontaneous NMDAR-mediated excitatory postsynaptic current amplitude in DGCs. These findings provide a mechanistic explanation for the antiseizure effects of glycolysis inhibition: 2-deoxyglucose and LDH inhibitors may suppress seizures in part by limiting lactate availability at HCAR1 in the dentate gyrus.

Disclosures: D. Gyamfi: None. **H. Sun:** None. **J. Kapur:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.05/T1

Topic: B.08. Epilepsy

Support: NIH R01 NS092552
T32GM144856

Title: Reactive Neuroplasticity in the Dorsal Motor Nucleus of the Vagus in a Mouse Model of Temporal Lobe Epilepsy and Tauopathy Reveals Circuit Mechanisms Underlying SUDEP Risk

Authors: *L. CANTU[1,2], M. MOSELEY[2], B. N. SMITH[2];
[1]Biomed. Sci., Colorado State Univ. Molecular, Cell. & Integrative Neurosciences, Fort Collins, CO; [2]Biomed. Sci., Colorado State Univ., Fort Collins, CO

Abstract: Hyperphosphorylated tau (pTau) is associated with epilepsy and increases neuronal network excitability, yet its contribution to Sudden Unexpected Death in Epilepsy (SUDEP)

remains unclear. SUDEP is thought to result from seizure-induced cardiorespiratory dysfunction, implicating autonomic brainstem circuits such as the dorsal vagal complex. We hypothesize that temporal lobe epilepsy (TLE) and tauopathy induce alterations in synaptic transmission and intrinsic excitability within brainstem autonomic circuits, specifically in the NTS-to-DMV pathway, that impair autonomic regulation. To examine the interaction between epilepsy and tauopathy, hTau mice expressing all 6 isoforms of normal human tau and non-transgenic control mice were given intrahippocampal kainate (IHK) injections to induce status epilepticus (SE) and, after a latent period, acquired TLE with spontaneous recurrent seizures (SRS). Seizure activity (during both SE and SRS) and survival were assessed by video monitoring, and whole-cell patch-clamp recordings were obtained from DMV neurons. hTau mice exhibited significantly higher rates of SUDEP compared to both tau knockout and non-transgenic C57BL/6J controls ($p < 0.0001$). Interestingly, we found a sex difference in hTau mice with females dying at higher rates than males ($p= 0.017$). Additionally, significantly increased frequencies of both sEPSCs and sIPSCs were observed in DMV neurons of hTau mice ($p= 0.0114$ and $p=0.0035$) with TLE compared to C57BL/6J controls, along with altered intrinsic excitability, suggesting enhanced synaptic drive and disrupted autonomic regulation in hTau mice with TLE. Together, these results indicate that human tau expression increases vulnerability to SUDEP and is associated with functional remodeling of DMV neurons. Altered synaptic and intrinsic properties within brainstem autonomic circuits may represent a mechanism by which tauopathy amplifies epilepsy-related cardiorespiratory dysfunction and SUDEP risk.

Disclosures: L. Cantu: None. **M. Moseley:** None. **B.N. Smith:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.06/T2

Topic: B.08. Epilepsy

Title: Ion Channel panel for assessing seizure risk

Authors: *P. MITCHELL, S. STABILINI, R. ABDELAZIZ;
IQVIA, Saffron Walden, United Kingdom

Abstract: Ion channels play a critical role in regulating cellular excitability and are a major class of off-targets associated with adverse drug effects, including seizure liability, making early identification of ion channel interactions essential for de-risking compounds in drug discovery. We developed a high-throughput ion channel screening panel using an automated patch clamp platform (Qube) to support early safety pharmacology by enabling efficient and reproducible evaluation of compound effects across key ion channels relevant to neuronal excitability, including voltage and ligand-gated ion channels. Compounds were tested using standardised electrophysiological protocols designed to detect modulatory effects. The platform demonstrated

robust assay performance with high reproducibility and reliability across targets, and compounds with known ion channel liabilities showed expected pharmacological profiles. This approach enables parallel, scalable screening across multiple ion channel targets, facilitating early identification of off-target interactions associated with seizure risk. Overall, this ion channel panel provides an efficient and scalable solution for early safety assessment, supporting improved decision-making and compound prioritisation in preclinical drug development

Disclosures: P. Mitchell: A. Employment/Salary (full or part-time):; IQVIA. **S. Stabilini:** A. Employment/Salary (full or part-time):; IQVIA. **R. Abdelaziz:** A. Employment/Salary (full or part-time):; IQVIA.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.07/T3

Topic: B.08. Epilepsy

Support: NIH Grant 1R01EB037718-01

Title: DNA-Aptamer Based Potassium Sensor for Investigating Neuronal Activity

Authors: *J. R. CRESSMAN;
George Mason Univ., Fairfax, VA

Abstract: A major bottleneck in studying focal epilepsy is the lack of non-invasive, in vivo modalities capable of measuring real-time potassium K+ dynamics—a core biophysical driver of neuronal hyperexcitability and epileptogenesis. Traditional metabolic mapping techniques, such as FDG-PET, fail to capture these active cellular mechanisms. To overcome this technical barrier, we developed DNA-aptamer-based potassium sensors designed to resolve localized K+ concentrations at the cellular level. These synthetic oligonucleotides undergo precise conformational changes upon potassium binding, translating ion concentrations into highly specific optical signals. We successfully delivered these biocompatible probes into the intracellular space of murine neurons in ex vivo preparations to monitor stimulation-induced changes in K+ concentrations. To transition this technology to in vivo applications, we are reengineering the probes to operate within the near-infrared II (NIR-II) optical window. This shift minimizes tissue autofluorescence and photon scattering, enabling deep-tissue imaging in the whole animal. This sensor platform allows researchers to bypass indirect metabolic proxies and invasive techniques. Ultimately, it provides a high-resolution window into the fundamental biophysical microenvironment driving tissue hyperexcitability and seizure generation.

Disclosures: J.R. Cressman: None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.08/T4

Topic: B.08. Epilepsy

Title: Repeated Zero-Mg^{2+} Seizure-Like Activity Selectively Disrupts Inhibitory Synaptic Organization in an In Vitro Model of Drug-Resistant Epilepsy

Authors: *U. ZAIDI[1], F. IQBAL[1], K. SHUKOOR[2], N. I. SYED[3], K. YUSUF[1];
[1]Univ. of Calgary, Calgary, AB, Canada; [2]Cumming Sch. of Med., Med. Univ. of the Americas, Calgary, AB, Canada; [3]Dept. Cell Biol. & Anat., Univ. Calgary, Calgary, AB, Canada

Abstract: Drug-resistant epilepsy (DRE) affects approximately 30% of epilepsy patients and carries severe neurodevelopmental consequences. Refractory status epilepticus (SE) represents an extreme form of pharmacoresistant seizure activity, in which progressive $GABA_A$ receptors, which are the primary targets of first-line benzodiazepines for SE-rescue, lead to desensitization to benzodiazepine-mediated intervention. However, it remains unclear whether these changes reflect structural loss of inhibitory synaptic organization or redistribution/internalization of receptor pools. Distinguishing between these possibilities is critical, as synaptic loss and receptor internalization carry different implications for the reversibility of DRE-associated pathology and the potential for pharmacological rescue.
To model cumulative SE-like excitotoxic burden, primary rat hippocampal neuron cultures (n=6 per condition) were subjected to repeated one-hour Mg^{2+}-free exposures from DIV 15 to DIV 20, with Mg^{2+}-containing solution serving as controls. Cultures were permeabilized prior to immunolabeling to quantify total $GABA_A$ receptor α1 subunit (GABAR) and PSD-95 expression, including internalized receptor pools, alongside neurofilament as a structural integrity marker. Three-dimensional puncta number, density, clustering, neurofilament-associated localization, and inhibitory-to-excitatory spatial coupling were quantified.
Repeated Mg^{2+}-free seizure-like activity selectively disrupted inhibitory synaptic marker organization and reduced the spatial coupling between GABAR and PSD-95 puncta, while excitatory postsynaptic architecture was relatively preserved. Notably, the reduced GABAR puncta number in permeabilized cultures, together with preserved within-cluster receptor density, supports a loss of inhibitory receptor puncta rather than receptor internalization alone. Together, these findings provide a three-dimensional spatial characterization of inhibitory synaptic disruption in the repeated Mg^{2+}-free DRE model and establish a structurally sensitive approach for evaluating anti-seizure medication-mediated synaptic preservation of synaptic organization.

Disclosures: U. Zaidi: None. **F. Iqbal:** None. **K. Shukoor:** None. **N.I. Syed:** None. **K. Yusuf:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.09/T5

Topic: B.08. Epilepsy

Title: Human iPSC-Derived Functional Neural Networks Enable Detection of Seizure Liability and Neurotoxicity

Authors: *S. HOLT[1], K.-C. PITSA[2], J. LAMB[4], S. SCHWENGBERG[1], S. JAIN[3];
[1]Ncardia Services B.V., Leiden, Netherlands; [2]Ncardia, Ncardia Services B.V., Netherlands; [3]Ncardia, Leiden, Netherlands; [4]Ncardia services B.V., Leiden, Netherlands

Abstract: Human induced pluripotent stem cell (iPSC)-derived neural cultures recapitulate key structural and functional features of the human central nervous system (CNS) and provide a physiologically relevant approach for evaluating CNS safety liabilities. The objective of this study was to develop human iPSC-derived functional assays capable of detecting therapeutic-induced network hyperexcitability and neurotoxicity relevant to CNS safety assessment. Human iPSC-derived neurons and astrocytes were co-cultured to establish functional neuronal networks compatible with high-throughput calcium imaging and multi-electrode array (MEA) electrophysiology. Calcium imaging assessed spontaneous calcium transients and network excitability, while MEA recordings characterized neuronal activity. Functional responses were evaluated across a panel of 70 preclinical candidates and compared with in vivo CNS toxicity findings. Neural cultures demonstrated stable and reproducible activity, with calcium imaging metrics exhibiting less than 15% inter-well variability. Screening identified distinct response profiles associated with differing levels of CNS risk. Highly toxic therapeutics produced marked suppression of calcium oscillations and were associated with seizures and convulsions in vivo. Therapies associated with milder neurological findings induced transient network perturbations followed by partial recovery, whereas non-toxic therapies maintained normal neuronal activity. Calcium imaging and MEA recordings identified electrophysiological signatures associated with seizure liability, including increased firing and burst frequency, enhanced network synchrony, and periods of hyperexcitability preceding loss of coordinated activity. Additional therapies induced reductions in spike amplitude and network burst frequency, consistent with impaired neuronal function and neurotoxicity. Calcium imaging endpoints demonstrated approximately 80% concordance with rodent CNS toxicity outcomes. Furthermore, optimization guided by these assays improved calcium oscillation scores by approximately 40% while preserving pharmacological activity. Collectively, these findings demonstrate that human iPSC-derived neuronal network assays can detect and differentiate therapy-induced seizure liability and neurotoxicity in a human-relevant system. Integration of calcium imaging and electrophysiological endpoints provides a translational framework for early identification of CNS safety liabilities and supports development of safer oligonucleotide therapeutics.

Disclosures: S. Holt: None. **K. Pitsa:** None. **J. Lamb:** None. **S. Schwengberg:** None. **S. Jain:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.10/T6

Topic: B.08. Epilepsy

Support: NIH Grant R01NS130042

Title: Medial ganglionic eminence-derived interneuron dysfunction drives seizures in a mouse model of KCNT1 developmental and epileptic encephalopathy.

Authors: *M. C. WESTON[1], A. SHORE[2], M. SAFARI[3];
[1]Fralin Biomed. at Virginia Tech., Roanoke, VA; [2]Fralin Biomed. Res. Inst., Roanoke, VA; [3]Virginia Tech., Roanoke, VA

Abstract: Normal 0 false false false EN-US JA HE /* Style Definitions */ table.MsoNormalTable {mso-style-name:"Table Normal"; mso-tstyle-rowband-size:0; mso-tstyle-colband-size:0; mso-style-noshow:yes; mso-style-priority:99; mso-style-parent:""; mso-padding-alt:0in 5.4pt 0in 5.4pt; mso-para-margin-top:0in; mso-para-margin-right:0in; mso-para-margin-bottom:8.0pt; mso-para-margin-left:0in; line-height:107%; mso-pagination:widow-orphan; font-size:11.0pt; font-family:"Calibri",sans-serif; mso-ascii-font-family:Calibri; mso-ascii-theme-font:minor-latin; mso-hansi-font-family:Calibri; mso-hansi-theme-font:minor-latin; mso-bidi-font-family:Arial; mso-bidi-theme-font:minor-bidi;} Pathogenic variants in the sodium-activated potassium channel gene ***KCNT1*** cause severe early-onset epilepsies characterized by frequent, treatment-resistant seizures. Although these variants produce gain-of-function (GOF) increases in potassium current in several neuron types, the neuronal populations that drive seizures remain unknown. Here, we show that medial ganglionic eminence (MGE)-derived cortical interneurons (cINs), particularly those expressing **somatostatin, are selectively vulnerable to KCNT1 GOF**, leading to impaired cortical inhibition and seizure generation. Using a knock-in mouse model carrying the epilepsy-associated ***Kcnt1* R409Q** variant (R428Q in humans), we identify severe seizure activity accompanied by altered cortical network state dynamics. Electrophysiological recordings reveal increased KCNT1-mediated currents and reduced intrinsic excitability selectively in **cINs**, with the strongest effects in **somatostatin-expressing cINs**. Conditional expression of the variant in *Nkx2.1*-expressing neurons, the bulk of which are **PV- and SST-expressing, MGE-derived forebrain interneurons,** is sufficient to reproduce the severe seizure phenotype, including multiple seizure types and a highly disrupted interictal EEG, and to increase SUDEP risk. Consistent with this mechanism, KCNT1 GOF disrupts SST synaptic output to layer 2/3 pyramidal neurons in anterior motor cortex. These findings identify **somatostatin interneuron dysfunction as a key cellular mechanism of *KCNT1*-related epilepsy** and reveal selective vulnerability of cortical inhibitory circuits to KCNT1 GOF.

Disclosures: M.C. Weston: None. **A. Shore:** None. **M. Safari:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.11/T7

Topic: B.08. Epilepsy

Support: Department of Biotechnology, Ministry of Science and Technology, Government of India

Title: Mechanistic Insights into CDK5-Dependent Synaptic Alterations in Focal Cortical Dysplasia

Authors: *A. TYAGI[1], S. SWEETY[2], J. BANERJEE[4], M. TRIPATHI[5], P. CHANDRA[6], A. B. DIXIT[3];
[1]Dr. B. R. Ambedkar Ctr. for Biomed. Research, Univ. of Delhi, New Delhi, India; [2]ACBR, Univ. of Delhi, New Delhi, India; [3]ACBR, ACBR, Univ. of Delhi, Delhi, India; [4]Biophysics, All India Inst. of Med. Sci. (AIIMS), New Delhi, India, New Delhi Delhi, India; [5]Dept. of Neurol., [6]Dept. of Neurosurg., All India Inst. of Med. Sci. (AIIMS), New Delhi, India, New Delhi, India

Abstract: Focal cortical dysplasia (FCD) is a malformation of cortical development and one of the leading causes of drug-resistant epilepsy in both pediatric and adult populations. It is characterized by abnormal cortical lamination and defects in neuronal migration, growth, and differentiation, resulting in the formation of hyperexcitable neuronal networks. Cyclin-dependent kinase 5 (CDK5), a neuron-specific serine/threonine kinase, plays a pivotal role in neuronal migration, synaptic plasticity, neurotransmission, and circuit formation. CDK5 has a broad range of substrates including a large number of synaptic proteins. Gephyrin is the postsynaptic scaffold protein at inhibitory synapses that plays an essential role in the stability of gephyrin-dependent GABAA receptor clusters. Given the critical role of CDK5 in regulating synaptic plasticity, and network organization, the present study was undertaken to investigate its expression and activity in FCD and to elucidate its potential contribution to epileptogenesis and aberrant neuronal circuit formation Brain tissue specimens from the frontal and temporal lobes of patients with focal cortical dysplasia (FCD; n = 23) were obtained during epilepsy surgery. Region-matched autopsy brain tissues from individuals without a history of seizures or other neurological disorders (n = 15) served as non-epileptic controls. Histopathological validation was performed using hematoxylin and eosin (H&E) staining. Protein expression of Cdk5, p-Cdk5, gephyrin, p-gephyrin, γ2 containing GABAA receptor in FCD was studied by western blotting. Co-expression analysis of Gephyrin and γ2 containing GABAA receptor was carried out by immunofluorescence in patients with FCD. Histopathological analysis validated FCD pathology in patient samples, while non-seizure autopsy controls exhibited normal cortical architecture. Western blot analysis revealed significantly increased levels of phosphorylated CDK5, gephyrin,

phosphorylated gephyrin, and GABAA receptor γ2 subunits in FCD tissues. Consistently, immunofluorescence studies demonstrated enhanced co-localization of gephyrin and GABAA receptor γ2 in FCD compared to control. These findings suggest that dysregulation of CDK5 signaling is associated with contributing to the pathophysiology of FCD. It might have a potential role in increasing the stability of gephyrin-dependent γ2 subunit containing GABAA receptor clusters in FCD. The observed changes may contribute to aberrant circuit formation and epileptogenesis, highlighting CDK5 as a potential molecular target for understanding and treating FCD-associated epilepsy.

Disclosures: A. Tyagi: None. **S. Sweety:** None. **J. Banerjee:** None. **M. Tripathi:** None. **P. Chandra:** None. **A.B. Dixit:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.12/T8

Topic: B.08. Epilepsy

Support: NIH Grant R35NS143046

Title: Postnatal Deletion of Tsc2 from Cortical Somatostatin Neurons

Authors: *L. G. JEROW[1], C. L. LASARGE[2], C. MCCOY[5], M. DUSING[3], S. C. DANZER[4]; [1]Neurosci. Grad. Program, Univ. of Cincinnati, Cincinnati, OH; [2]Anesthesia, [4]Dept Anesthesia, [3]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [5]Neurosurg., Cincinnati Children's Hosp., Cincinnati, OH

Abstract: Tuberous sclerosis complex (TSC) is a neurocutaneous disorder affecting nearly 1 in 6,000 individuals, with epilepsy being the most common neurological symptom. TSC occurs from mutations to either the TSC1 or TSC2 genes, resulting in hyperactivation of the mTOR pathway. TSC is believed to be a disorder occurring from mutations within radial glial progenitor cells producing excitatory neurons. However, recent research has shown the involvement of interneurons in some patients. Whether interneuron involvement alters disease phenotype is unknown. Previously, we developed a model of TSC with a focal deletion of *Tsc2* from excitatory neurons. Here we generate a new model deleting *Tsc2* from somatostatin (SST)-expressing neurons to assess the role of interneurons in TSC. To delete *Tsc2* from SST interneurons, a triple transgenic (SST-FlpO, tdTomato (tdT) reporter, $Tsc2^{fl/fl}$) dual viral injection approach was developed. To target SST interneurons, Flp recombinase was expressed in SST neurons using SST-FlpO mice, leading to *Tsc2* deletion via Flp-dependent AAV9-CAG-Frt-Cre/HA infection. To simultaneously label excitatory neurons for anatomical analyses, AAV9-CaMKII-EGFP was used. With this approach, SST neurons are tagged with hemagglutinin (HA) and tdTomato, and excitatory neurons with eGFP. The AAVs were infused

on postnatal day 2 (P2) via bilateral injections (100nl each) of mixed AAV9-CAG-Frt-Cre/HA + AAV9-CaMKII-EGFP into frontal cortex. SST-FlpO$^{+/-}$, Tdt$^{+/-}$, Tsc2$^{wt/wt}$ mice served as controls. At 8-12 weeks old, mice were implanted with cortical electrodes and underwent at least one week of 24/7 video-EEG monitoring before tissue was collected. AAVs produced high infectivity of inhibitory neurons, labeling 79.5-90.5% of SST cells in the injected region. Deletion of *Tsc2* led to somatic hypertrophy and sprouting of virally infected SST cells, consistent with the growth-promoting effects of mTOR hyperactivation. No seizures were observed in study mice. Further histological analyses will be required to examine lesion composition and size. However, these findings suggest that loss of *Tsc2* in SST interneurons alone is not sufficient to drive epileptogenesis.

Disclosures: L.G. Jerow: None. **C.L. LaSarge:** None. **C. McCoy:** None. **M. dusing:** None. **S.C. Danzer:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.13/T9

Topic: B.08. Epilepsy

Title: Characterizing Cortical Development and Network Dysfunction in a Mouse Model of Focal Cortical Dysplasia

Authors: *A. EDWARDS[1], A. K. SRIVASTAVA[4], K. HASHIMOTO-TORII[2], M. TORII[3]; [1]Children's Natl. Hosp., Silver Spring, MD; [2]Children's Natl. Hosp., Children's National Hospital, DC; [3]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC; [4]Ctr. for Neurosci. Res., Childrens Natl. Med. Ctr., Washington DC, DC

Abstract: Focal cortical dysplasia type II (FCD II) is a leading cause of drug-resistant epilepsy, yet the developmental timeline and cellular consequences of somatic mutations remain poorly defined. Using in utero electroporation to express the FCD II-associated mutant PIK3CA-E545K in the developing cerebral cortex, we investigated its effects on interneuron populations and neuronal morphology. We also examined the long-term efficacy of GABAergic progenitor cell transplantation. Adult dysplastic cortex exhibited a significant reduction in interneuron density despite mutant expression being restricted to excitatory neurons, indicating a non-cell-autonomous effect on inhibitory circuit development. Developmental analysis revealed a transient increase in TUNEL-positive cells at E15, one day after electroporation, which resolved by E17, suggesting that PIK3CA-E545K disrupts cortical development within 24 hours of expression. Morphological characterization demonstrated that mature PIK3CA-E545K-expressing neurons exhibited enlarged and more heterogeneous somata, increased dendritic complexity due to a greater number of primary neurites, and a proximal shift in dendritic distribution. These structural abnormalities are consistent with the formation of aberrant local

excitatory networks that may contribute to epileptogenesis. Transplantation of medial ganglionic eminence-derived GABAergic progenitor cells at P30 suppressed seizures for up to 123 days; however, seizure frequency and duration subsequently increased despite transplanted cells remaining largely confined to the dysplastic region. Together, these findings identify early, non-cell-autonomous developmental effects of PIK3CA-E545K, reveal persistent alterations in neuronal architecture, and demonstrate that GABAergic cell therapy can provide substantial but incomplete long-term seizure suppression in this model of FCD II.

Disclosures: A. Edwards: None. **A.K. Srivastava:** None. **K. Hashimoto-Torii:** None. **M. Torii:** None.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.14/T10

Topic: B.08. Epilepsy

Title: Selective elimination of inhibitory hub neurons suppresses epileptic network activity

Authors: T. LORINCZ, B. KOCSIS, ***N. LENKEY**, B. ROZSA;
BrainVisionCenter Res. Inst. and Competence Ctr., Budapest, Hungary

Abstract: Surgical resection remains the only permanent treatment option for many patients with drug-resistant focal epilepsy. However, its applicability is limited by the invasiveness of the procedure and by the difficulty of precisely delineating seizure-generating regions. Here, we present a cellular-resolution approach for identifying and selectively targeting critical components of the epileptic network based on its functional microstructure. Using simultaneous electrophysiological (LFP) recordings and acousto-optic two-photon Calcium imaging of inhibitory neurons in the kainite-induced mouse model of focal cortical epilepsy (n = 9 Bl/6 mice; 44-117 neurons per session) we found that interneurons in the posterior parietal cortex formed stable clusters associated with interictal epileptiform discharges (IEDs). We found typically 4-7 clusters in each animal, which exhibited distinct firing motifs around IED and remained consistent across recording sessions. Although the cluster organization partially reflected the correlation structure observed during IED-free spontaneous activity, IED-related recruitment substantially reshaped these relationships, indicating that IEDs engage a unique interneuronal network architecture. Based on these observations, we identified highly interconnected correlative hub cells, typically 10-15% of the imaged interneurons and selectively ablated them by using brief two-photon laser pulses. We eliminated only a small number of inhibitory hub cells (2-5 cells per mice out of 5-11 target cells), which induced a robust long-term reduction in IED frequency following a transient period of fluctuating network activity (n = 6 animals). This intervention desynchronized the previously highly correlated interneuronal network, and substantially changed the cluster structure mapped in the Principal Component

Analysis space. Our findings suggest that epileptic networks contain functionally defined inhibitory hub cells that disproportionately contribute to pathological activity. Identification and selective elimination of these cells may provide the basis for a novel diagnostic and therapeutic strategy for focal epilepsies, enabling highly specific intervention while preserving the integrity and function of the broader neuronal network.

Disclosures: T. Lorincz: None. **B. Kocsis:** None. **N. Lenkey:** None. **B. Rozsa:** Other; A founder of Femtonics and a member of its scientific advisory board., Femtonics Ltd.

Poster

PSTR258: Epilepsy Mechanisms: Channels, Synapses, Interneurons, and Developmental Dysfunction

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR258.15/T11

Topic: A.06. Developmental Disorders

Support: NICHD HD008962 (T.J.P.)
NICHD Intramural Research Fellowship

Title: Spatiotemporal transcriptome reveals fate alteration and non-cell autonomous response in X-linked epilepsy models

Authors: *J. LI, V. GARG, A. TANZILLO, Y. ZHANG, T. J. PETROS;
NICHD/Eunice Kennedy Shriver Natl. Inst. of Child Hlth. and Human Develop., Bethesda, MD

Abstract: Arx (Aristaless-related homeobox) is an X-linked transcription factor that is expressed in inhibitory neurons within the ganglionic eminences as they exit the cell cycle. In humans, ARX variants are one of the leading causes of several distinct X-linked intellectual disabilities (XLID) and related syndromes. Notably, recent clinical evidence indicates that >50% of heterozygous female carriers of ARX variants also display mild to severe phenotypes. Loss of Arx results in aberrant interneuron differentiation & cell migration, with many models displaying infantile spasms and epilepsy. Here we generated *Nkx2.1-Cre;Arx*$^{F/Y}$ cKO males and *Nkx2.1-Cre;Arx*$^{F/+}$ heterozygous (Het) females to remove Arx in MGE-derived neurons. The cKO male mice displayed severe phenotypes with spasms and epilepsy, likely recapitulating X-linked myoclonic seizures. Het female mice displayed mild to moderate anxiety and locomotor defect, mimicking symptoms of Partington syndrome. We observe significant reduction in PV+ and SST+ interneurons in these both cKO males and Het females, leading to increased seizure susceptibility. We performed single cell sequencing and spatial transcriptomics to identify genetic and cellular changes in embryonic and adult mice. In embryonic Arx cKO male mice, distinct cell clusters are completely lost and novel clusters appeared, whereas het females displayed both normal and novel cell clusters. In adult mice, we observed dysregulation of many neuropeptides in CA3 of cKO males, which likely modulates neuronal excitability and contributes to epileptogenesis. In addition, we identified non-cell autonomous transcriptional

changes in excitatory cortical neurons in both sexes. Overall, we uncovered distinct behavior and transcription changes in Arx cKO males and Het females, likely underlying distinct phenotypes in patients.

Disclosures: J. Li: None. **V. Garg:** None. **A. Tanzillo:** None. **Y. Zhang:** None. **T.J. Petros:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.01/T12

Topic: B.08. Epilepsy

Support: NIA R01AG067788
NIGMS T32GM159560

Title: Investigating kainic acid-induced chronic spontaneous seizure susceptibility in Alzheimer's disease associated presenilin 2 KO mice

Authors: *L. ROBINSON-COOPER[1,2], I. ERICKSON[2], S. DAVIDSON[2], B. SANDERS[2], E. SADLER[2], M. L. BARKER-HALISKI[2,1];
[1]Grad. Program in Neurosci., [2]Dept. of Pharmaceutics, Univ. of Washington, Seattle, WA

Abstract: Background: Presenilin 2 (**PSEN2**) gene variants increase early-onset Alzheimer's disease (**EOAD**) risk. EOAD patients with PSEN2 variants have increased seizure risk versus age-matched healthy controls, with seizures altogether worsening functional and cognitive decline (Zawar et al, 2025). However, few studies have interrogated PSEN2 contributions to seizure risk. While the canonical hallmark of AD is amyloid-β (**Aβ**) plaque deposition, PSEN2 variant models do not exhibit Aβ plaques, allowing mechanistic study of Aβ-independent contributions to AD burden. We have earlier reported that 3-4-month-old PSEN2 knockout (**KO**) mice are more prone to acute kainic acid (**KA**)-induced seizures, a naturally occurring glutamate receptor agonist, versus age-matched wild-type (**WT**) mice (Robinson-Cooper, Davidson, et al. 2025). Low dose KA administration also induces chronic spontaneous recurrent seizures (**SRS**) onset to model acquired epilepsy. Given that young PSEN2 KO mice are more prone to KA-induced seizures, we hypothesized that PSEN2 KO mice would have earlier SRS onset, and greater chronic SRS burden, thus providing a platform to identify novel mechanistic contributors to AD burden. **Method:** 3-4-month-old male and female PSEN2 KO and WT mice (n = 14 PSEN2 KO and n = 20 WT) were given repeated low dose KA (2.5-7.5 mg/kg, i.p.) until onset of sustained generalized seizures. After KA, surviving mice (n = 3 PSEN2 KO and n = 10 WT) recovered for 1 week before surface EEG electrodes implantation for subsequent video-EEG (**vEEG**) monitoring beginning one week later. Mice were continuously vEEG recorded for SRS onset and severity for 3 weeks. Raw EEG data was processed for seizure detection, and all SRS

activity scored on a modified Racine scale. **Results:** In the chronic monitoring period post-KA-SE only male WT mice (n = 4) presented with SRS. Female WT mice (n =6) and PSEN2 KO mice (n = 3) did not exhibit SRS during the 3-week recording period. As none of the male PSEN2 KO mice survived acute KA-SE, none was available for vEEG recording. Male WT mice had an average cumulative seizure burden of 39.25 ± 14.7, calculated by adding the Racine scale score of each seizure over the 3-week period. Analysis of seizure frequency and severity, including male PSEN2 KO mice, will be further discussed. **Conclusions:** Among post-KA SE WT mice, only males experienced spontaneous seizures in the monitoring period. Previous studies investigating chronic spontaneous seizures induced by KA-SE in C57BL/6J mice have only used males (Puttachary et al 2015, Umpierre et al 2016), thus the present results may represent a previously unreported sex difference in the KA SE mouse model of chronic epilepsy.

Disclosures: L. Robinson-Cooper: None. **I. Erickson:** None. **S. Davidson:** None. **B. Sanders:** None. **E. Sadler:** None. **M.L. Barker-Haliski:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.02/T13

Topic: B.08. Epilepsy

Support: Kenneth Eisenberg Emerging Scholar Award

Title: Development of an On-Demand Preclinical Model of the Postictal State

Authors: *A. NOOR[1], S. ABBASI[1], J. BARDEN[1], A. HERMAN[2], J. MATTIS[1];
[1]Neurol., [2]Univ. of Michigan, Ann Arbor, MI

Abstract: The postictal state, the period spanning from seizure cessation to return to baseline, is characterized by a range of signs and symptoms including EEG slowing and attenuation, impaired arousal, and cognitive and behavioral deficits. This postictal state is typically significantly longer than the precipitating seizure, and many patients rate it as the most burdensome aspect of their epilepsy, but we nevertheless lack targeted therapeutic tools to ameliorate it. Progress on this front has been limited by the absence of reliable preclinical models. The *Scn1a*$^{+/-}$ mouse model of Dravet Syndrome is well-characterized as an epilepsy model and has the experimentally advantageous feature of naturalistic seizures that can be triggered on-demand via hyperthermia. We postulated that *Scn1a*$^{+/-}$ mice could similarly serve as an on-demand postictal model, and we here sought to characterize their behavior in the postictal period. Hyperthermic seizures were acutely triggered in *Scn1a*$^{+/-}$ mice using a heat lamp placed over the induction chamber. Each *Scn1a*$^{+/-}$ mouse was heated in tandem with two wildtype (WT) mice: (1) a littermate used as a control for heating, and (2) a mouse in which a rectal temperature probe was secured. All mice were heated until behavioral seizure onset (in the *Scn1a*$^{+/-}$ mouse)

or internal body temperature measurement of 42.5 °C (of the probe mouse); the *Scn1a*$^{+/-}$ and WT control mice were then transferred to opaque, room-temperature recording chambers for 1 hour of video recording. Analysis was performed using LabGym, an AI-based software used to identify and measure behaviors. LabGym's motion-tracking software was used to analyze distance traveled, and the categorizer software was used to distinguish between immobility and quiet wakefulness. The postictal state in adult *Scn1a*$^{+/-}$ mice was reliably characterized by a significant reduction in spontaneous locomotion and further reduction of the quiet wakefulness state compared to heated WT controls. Preliminary analyses across successive seizures suggest a stable within-mouse phenotype in adult mice. Additional analyses to characterize effects of age, sex, and pharmacologic manipulation are ongoing. In sum, this model phenocopies the reduced behavioral output that is a key clinical feature of the postictal state, providing an experimentally tractable, on-demand platform for the testing of interventions to reduce postictal symptom burden.

Disclosures: A. Noor: None. **S. Abbasi:** None. **J. Barden:** None. **A. Herman:** None. **J. Mattis:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.03/T14

Topic: B.08. Epilepsy

Title: Mechanism of status epilepticus-induced microglial-dendritic interactions.

Authors: *P. MASSA, U. B. EYO;
Univ. of Virginia, Charlottesville, VA

Abstract: Status epilepticus is defined as seizures lasting over 5 minutes or repeated seizures without recovery of consciousness between episodes. When poorly controlled, this common health emergency often results in lasting neuronal damage manifesting as physical disability or even death. First line therapeutics target imbalances in neuronal excitation but are not always effective and refractory epilepsy remains a common and costly issue prompting the search for novel mechanisms of status epilepticus control. Microglia, the brain's resident immune cells, pose a conceivable target for development of new therapies as they play several roles impacting the development and recovery from status epilepticus such as but not limited to synaptic pruning, inflammation regulation, and neurogenesis. Using real-time in vivo two photon imaging following status epilepticus, we previously discovered a novel microglial dynamic state where microglia form process pouches that target but don't engulf beaded neuronal dendrites. In search of molecular regulators of and a functional significance for these interactions, we identify MerTK receptors as a necessary promoter of this behavior. Furthermore, microglia pouches are associated with better resolution of beaded dendrites prompting our current hypothesis that

microglia MerTK responds to neuronal signaling to promote recovery post severe seizures. In this study we aim to (1) test this hypothesis further using conditional genetic approaches, (2) interrogate functional outcomes based on microglia ability to form pouch, and (3) further elucidate the molecular mechanism behind pouch formation.

Disclosures: P. Massa: None. **U.B. Eyo:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.04/T15

Topic: B.08. Epilepsy

Support: Savoy Foundation
NSERC
CFI

Title: Chemogenetic reactivation of hippocampal engrams can reverse memory impairments following chronic pentylenetetrazol kindled seizures

Authors: *S. M. SISSONS[1,2], H. LEHMANN[1], N. M. FOURNIER[1];
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Abstract: Epilepsy is a chronic neurological disorder characterized by recurrent seizures and cognitive impairments. Up to 50% of people with epilepsy experience persistent memory deficits underscoring the need to develop novel treatments. A memory engram refers to a specific subset of neurons recruited during learning that undergo modifications which promotes their reactivation during later memory recall. Pathological neuronal activity can disrupt the formation of engram connectivity which is believed to contribute to impaired memory recall after seizures. However, it remains unclear whether disrupted engram reactivation directly contributes to epilepsy-related cognitive impairments. To investigate mechanisms that contribute to seizure-induced memory deficits, rats underwent contextual fear conditioning over three days to associate a specific context with a footshock. Contextual fear conditioning resulted in elevated freezing responses indicative learning with quantification of the immediate early gene product c-Fos showing peak expression on the second day of conditioning supporting this time point for subsequent engram targeting. We then used an activity-dependent neuronal tagging approach that combined Fos-TRAP and chemogenetics to selectively capture and manipulate CA1 hippocampal memory engrams formed during contextual fear conditioning. Following engram tagging, rats underwent pentylenetetrazol-induced seizures or received vehicle injections over a three-week period. Compared with vehicle-treated controls, rats that experienced multiple PTZ-evoked seizures showed significant impairments in contextual fear memory recall. However, chemogenetic reactivation of the originally tagged memory engrams was sufficient to rescue the

memory deficits associated with PTZ seizures. These findings suggest that memory engrams remain partially intact despite pathological circuit remodelling following chronic seizures. Taken together, our results further suggest that seizure-related memory deficits reflect impaired access to stored memory traces rather than permanent memory loss, raising the possibility that these memories may remain recoverable through targeted engram reactivation.

Disclosures: S.M. Sissons: None. **H. Lehmann:** None. **N.M. Fournier:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.05/T16

Topic: B.08. Epilepsy

Title: Docosahexaenoic acid protects canine neuron-like cells and attenuates seizure-related activities in a spontaneous epilepsy mouse model

Authors: C. MARASIGAN[1,2], Y. LEI[1], S. MAEDA[1], Y. MOMOI[1], *T. YONEZAWA[1]; [1]Grad. Sch. of Agr. and Life Sciences, The Univ. of Tokyo, Tokyo, Japan; [2]Dept. of Vet. Paraclinical Sciences, Univ. of the Philippines Los Baños, Laguna, Philippines

Abstract: Docosahexaenoic acid (DHA) is a critical component of neuronal membranes and plays vital roles in membrane structure and multiple neuromodulatory pathways. In many *in vitro* and clinical settings, DHA has demonstrated its antioxidative potential and antiepileptic properties by suppressing neuronal excitability. In murine models, a modulated seizure threshold and the reversion of drug tolerance in a pharmacologically resistant model by DHA have been documented. However, seizure-induced models do not fully reflect the intrinsic network dysfunction that is often seen in epilepsy, limiting their translational relevance. In this study, we demonstrated the protective effects of DHA acting as a structural component of canine glial- and neuron-like cells against lipid peroxidation, and evaluated the effects of orally administered DHA in the EL mouse epilepsy model. When cells were exposed to tert-butyl hydroperoxide (TBHP), the DHA-enriched group exhibited greater viability compared with the controls. By demonstrating the changes in the cell membrane, we found that DHA retains well-distributed, intact lipid membranes in J3T cells, suggesting structural protection against lipid peroxidation. *In vivo*, oral DHA supplementation did not alter the morphometric profile compared with that of the control groups. However, we find that DHA supplementation affected their convulsive behaviors, resulting in reduced seizure scores and prolonged latency to seizure onset. Consequently, we preliminarily analyzed changes in the brain gene expression profile using a targeted gene approach. We found that DHA downregulates brain mRNA expression of *Aqp4, Iba1, Gad65, Gad67,* and *mGluR5*, suggesting normalization of seizure-related genes in EL mice after treatment. Immunofluorescence analysis further confirmed changes in the expression of these markers, particularly in Gad65/67 and mGluR5, in DHA-treated brain tissues.

Interestingly, we observed evidence of impaired lipid peroxidation in the EL mouse model, a key element consistently modulated by DHA in both our *in vitro* and *in vivo* studies. Collectively, our findings provide preliminary evidence that DHA partially restores redox homeostasis, resulting in neuroprotection and reduced seizure-related activities in canine glial- and neuron-like cells and in a spontaneous epileptic mouse model, respectively.

Disclosures: C. Marasigan: None. **Y. Lei:** None. **S. Maeda:** None. **Y. Momoi:** None. **T. Yonezawa:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.06/T17

Topic: B.08. Epilepsy

Title: hAPP-J20 mice: a reliable model to study the intersection of the pathology of seizure and Alzheimer's disease

Authors: *W. GNIADZIK, S. NADERI, J. WILLIAMSON, J. KAPUR;
Neurol., Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid beta (Aβ) plaques and neurofibrillary tau tangles, which drive synaptic dysfunction and neuronal loss. AD patients have a higher risk of seizures compared to people who do not have AD. Aβ lowers the excitability threshold, contributing to aberrant neuronal network activity and making circuits more prone to epileptiform discharges. However, the underlying molecular mechanisms by which Aβ promotes seizure susceptibility remain poorly understood. We used J20 mice expressing the Swedish and Indiana APP mutations, a transgenic model particularly useful for investigating seizures in amyloid pathology. Animals were stereotaxically implanted with EEG electrodes. After one week of recovery, seizure outcomes (duration, frequency) and severity by behavioral seizure score (BSS) were measured using a video-EEG monitoring system. Additionally, genetically encoded calcium indicator (GCaMP7) was stereotaxically delivered to hippocampal CA1 neurons of C57BL/6 and J20 mice. GCaMP7 imaging was performed in acute brain slices to measure neuronal activity. In one cohort of J20 animals (n=8), we observed frequent spontaneous seizures, which were suppressed by memantine. The second cohort monitored at 2 and 4 months displayed seizures at 4 months. Hippocampal CA1 neurons of injected C57BL/6 mice showed robust spontaneous firing activity in response to increasing extracellular K+ concentrations. We expect to find that J20 mice will exhibit elevated neuronal firing frequency measured by calcium imaging, compared to C57BL/6 controls. Overall, we conclude that the J20 mouse is a useful model to study neuronal hyperexcitability in AD.

Disclosures: W. Gniadzik: None. **S. Naderi:** None. **J. Williamson:** None. **J. Kapur:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.07/T18

Topic: B.08. Epilepsy

Title: Bee Venom Reduces the Duration of 4-Aminopyridine-Induced Convulsive Seizures in Rats

Authors: *F. ROMERO-AVILA[1], C. VENTURA[2], L. G. MEDINA-CEJA[3], O. VARGAS[4]; [1]Univ. de Guadalajara, Guadalajara, Mexico; [2]Dept. de Biología Celular y Molecular, CUCBA, [3]Dept. of Cell. and Mol. Biol., [4]Univ. de Guadalajara, Zapopan, Mexico

Abstract: Epilepsy is a neurological disorder marked by persistent, synchronized neuronal discharges and often resistant to conventional antiseizure treatments. Animal models, such as those using 4-aminopyridine (4-AP), a potassium channel blocker that induces seizures by enhancing synaptic transmission, are essential for studying seizure mechanisms. Bee venom (BV) from Hymenoptera insects contains bioactive compounds with neuroprotective and anti-inflammatory properties, offering potential for novel therapeutic approaches in epilepsy and related neurodegenerative diseases.In this study, we evaluated the effects of BV on convulsive seizures in male Wistar rats. Seizures were induced by intracerebroventricular administration of 4-AP, followed 30 minutes later by subcutaneous administration of BV. For this purpose, animals were implanted with a guide cannula for drug delivery. Rats were randomly assigned to one of four groups (n=3 for each control groups and n=6 for experimental group): (1) control (0.9% NaCl), (2) 4-AP (20 mM), (3) control BV (10 µg), and (4) 4-AP + BV. Convulsive behavior was monitored and evaluated using the Racine scale for 3 hours post-administration, stages 3 to 5 considered indicative of convulsive seizures. On the following day, rats were perfused, and brain tissue was sectioned (20µm thickness) and processed with Nissl staining. Images of the hippocampal CA1, CA3, and dentate gyrus (DG) regions were captured in triplicate at 40x total magnification and analyzed via ImageJ for cell counting.The control and BV treated groups did not exhibit seizure behavior, compared to the 4-AP group, which observed intense seizures (stages 4-5). The seizure duration was markedly reduced in the 4-AP+BV group (56.67 ± 46.76 minutes) relative to the 4-AP group (170 ± 10 minutes). Regarding cell counts (Mean ± SD), we found no trend towards loss of cell quantity, either among the different groups or regions: CA1 (Control: 461.33 ± 67.78; 4-AP: 426 ± 94.73; BV: 434.33 ± 37.91; 4-AP+BV: 412.55 ± 81.87), CA3 (Control: 507.22 ± 49.21; 4-AP: 442.6 ± 80.64; BV: 463.66 ± 40.68; 4-AP+BV: 442.33 ± 83.38), and DG (Control: 429.77 ± 38.5; 4-AP: 417.44 ± 51.51; BV: 393.67 ± 56.79; 4-AP+BV: 440.55 ± 71.47). These results suggest that BV has the potential to attenuate both the severity and duration of seizures, however no clear trend towards loss was observed, with only 24 hours 4-AP post-administration.Although BV has not yet been widely explored as a treatment for epilepsy, its effects on seizure modulation requires further investigation,

particularly regarding its mechanisms of action within the nervous system. Supported by University of Guadalajara (PROSNI 2025, CVM/LGMC).

Disclosures: F. Romero-Avila: None. **C. Ventura:** None. **L.G. Medina-Ceja:** None. **O. Vargas:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.08/T19

Topic: B.08. Epilepsy

Title: Using a fly model of human migraine mutations ("flygraine") to identify novel modifiers of neuronal excitability

Authors: D. J. ZWIEFELHOFER[1], *C. FRANK[2];
[1]Anat. and Cell Biol., [2]Univ. of Iowa, Iowa City, IA

Abstract: Neurons are dynamic. If neuronal firing and transmission are not tightly regulated, then cell-cell communication is uncontrolled. This problem is accentuated in episodic conditions like epilepsy and migraine. These conditions are difficult to manage, and we need better understanding of neuronal function on cellular and genetic levels to gain new insights in how to address them. Simple models can offer novel insights. We engineered familial hemiplegic migraine (FHM1) mutations in *Drosophila melanogaster* Ca_V2/Cacophony. We characterized these mutations, using amino-acid substitutions in fly homologous to FHM1 substitutions R135Q and S161L. We generated a *Drosophila* stock carrying both FHM1 mutations, cac^{FHM1}. cac^{FHM1} shows coarse phenotypes reminiscent of rodent models of FHM1. These include high levels of lethality - and for the animals that do survive, phenotypes include uncoordinated movement, seizure susceptibility, and electrophysiological hyperexcitability. We are using genetics to identify behavioral and electrophysiological genetic modifiers of Ca_V2 gain-of-function/cac^{FHM1} phenotypes. We take a sequential approach: 1) identify loss-of-function genetic conditions that enhance or suppress cac^{FHM1} lethality; 2) from that pool of lethality modifiers, test if they enhance or suppress defects in seizure susceptibility, electrophysiological dysfunction, or synapse development. From a pilot screen of 122 signaling genes, we identified 10 loss-of-function conditions that are suppressors of cac^{FHM1} lethality and 10 that are enhancers. We are organizing our modifiers into distinct classes: **1)** Unexpectedly, some cac^{FHM1} lethality <u>enhancers</u> also <u>suppress</u> hyperexcitability. This profile happens when combining cac^{FHM1} with losses of function in factors that control intracellular Ca^{2+} signaling: phospholipase C-Beta (PLCβ), inositol trisphosphate receptors (IP_3R), ryanodine receptors (RyR) and Multiple inositol polyphosphate phosphatase 2 (Mipp2). It also happens when combining cac^{FHM1} with losses in GPCRs PDFR and Mthl1 and the GTPase activating protein, Tumbleweed. **2)** Some cac^{FHM1} lethality <u>enhancers</u> show <u>synapse growth phenotypes</u>. We see this phenotypic profile when

combining *cac*^{FHM1} with losses in some *Drosophila* GPCRs, like AKHR. **3)** Some *cac*^{FHM1} lethality suppressors also suppress hyperexcitability. We see this phenotypic profile when combining *cac*^{FHM1} with losses in the nucleosome remodeling factor NURF-38 and the GPCR AstC-R2. We present our current understanding of how these factors are behaving on a cellular level, as well as the full complement of modifiers we have identified in our ongoing screen.

Disclosures: D.J. Zwiefelhofer: None. **C. Frank:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.09/T20

Topic: B.08. Epilepsy

Title: Polyunsaturated fatty acids limit seizure severity in a Drosophila seizure model

Authors: N. PAYNE, *A. C. BELLEMER;
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Abstract: Epilepsy is a neurological disorder characterized by recurring seizures that affects millions of people around the world. Effective treatment for epilepsy is limited by the heterogeneous pathogenesis of the disorder as well as by the efficacy and side effects associated with existing medications. In this study, we use the *Drosophila melanogaster para*^{bss1} mutant as an experimental model of seizure disorders associated with voltage-gated sodium channel gene mutations. These mutants possess a point mutation in the para voltage-gated sodium channel gene that causes mechanically activated seizures, and the duration of these seizures can be used as a measure of seizure severity. We have found that supplementing the diet of these flies with fish oil rich in polyunsaturated fatty acids or with specific fatty acid compounds such as arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid significantly reduces seizure duration. In order to better understand the mechanism by which these compounds limit seizure severity, we are investigating the enzymes that are predicted to metabolize fatty acids. Preliminary analyses have focused on the Pxt enzyme, which shares 24.5% identity and active-site residues with human cyclooxygenase enzymes that produce prostaglandin molecules from arachidonic acid substrates. We show that Pxt has heme-dependent peroxidase activity *in vitro*, and ongoing experiments will address the potential fatty acid substrates of the enzyme along with its *in vivo* functionality. These studies may provide the basis for future clinical treatment of seizure disorder along with adding to our fundamental understanding of the factors that regulate neural excitability.

Disclosures: N. Payne: None. **A.C. Bellemer:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

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Program #/Poster #: PSTR259.10/T21

Topic: B.08. Epilepsy

Support: VA MERIT I01RX003498
DoD ERP IDA W81XWH-22-1-0287

Title: Epileptiform Activity and Hippocampal Hyperexcitability in a Pig Model of Chronic Traumatic Brain Injury

Authors: *B. MCCULLOUGH[1], M. ROSALINO[2], S. PENNACCHI[2], E. R. HALTER[3], E. MIRZAKHALILI[3], A. V. ULYANOVA[5], J. A. WOLF[4];
[1]Neurosurg., Univ. of Pennsylvania, Haddonfield, NJ; [3]Neurosurg., [2]Univ. of Pennsylvania, Philadelphia, PA; [4]Univ. of Pennsylvania, Wayne, PA; [5]Neurosurg., Perelman Sch. of Medicine, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Rationale: Traumatic brain injury (TBI) often leads to post-traumatic epilepsy, however the mechanisms and progression of these processes remain to be elucidated in gyrencephalic models. In addition, hyperexcitability in the hippocampus following TBI has been hypothesized to underlie cognitive deficits, yet measure of the progression of this process and correlations to the underlying electrophysiology have not been described. Methods: Yucatan miniature swine were injured or sham-injured at 6 months of age using controlled cortical impact (CCI). These pigs were then implanted with two depth electrodes (128, or 256 channels total) bilaterally covering both cortex and hippocampus and four bilaterally placed ECoG screws. Video-EEG was performed in the home cage 48 hours/week, with continuous video on the remaining days for up to one year post-injury. Manual and automated review for epileptiform activity in the cortex and hippocampus was performed, in addition to an assessment of changes in high-frequency oscillatory activity. Results: Using continuous video EEG monitoring, we observed consistent and recurrent patterns of epileptiform events, some of which lasted over 20 seconds, and were present following implantation. These SNW events often occur during state transitions to slow wave sleep, and were more prominent during non-REM sleep, and did not have strong behavioral correlates. Although these were unilateral injuries, events often began with a burst in the hippocampus and then involved both the contralateral hippocampus and then cortex, often bilaterally. The amplitude of HC bursts of activity were greatly increased in the injured animals in both hippocampi, and were present in the awake behaving animal. At times this progressed to spike and wave activity that was reflected on the ECoG screws. Contrary to expectations, both an automated machine learning approach and a manual review demonstrated a tapered curve of epileptiform event frequency and length of events in the many months post injury. High frequency oscillations (HFOs) were also detected, and substantially altered in injured vs. sham animals.Conclusion: These results indicate that unilateral CCI injury can induce chronic abnormal epileptiform events in both the cortex and hippocampus post injury. In

addition, unilateral injury quickly leads to contralateral hyperexcitability, and high-amplitude bilateral HC events may underlie aspects of cognitive dysfunction following TBI.

Disclosures: B. McCullough: None. **M. Rosalino:** None. **S. Pennacchi:** None. **E.R. Halter:** None. **E. Mirzakhalili:** None. **A.V. Ulyanova:** None. **J.A. Wolf:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.11/T22

Topic: B.08. Epilepsy

Support: VIEP-BUAP 2026
SECIHTI fellow No. CVU: 108308.

Title: Testosterone modulates absence seizures in the taiep rat

Authors: *R. CASTILLO[1], C. CORTES[2], A. UGARTE[3], J. R. EGUIBAR, Sr.[4];
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Abstract: The *taiep* rat was obtained at the Institute of Physiology-Benemérita Universidad Autónoma de Puebla. This is the first animal model of the human leukodystrophy named hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC). Magnetic resonance imaging (MRI) studies have shown ventriculomegaly, hypomyelination, and atrophy of the putamen and cerebellum. In addition, *taiep* rats have spike wave discharges (SWDs) in the electroencephalogram (EEG), resembling those reported in humans with absence seizures. These SWDs are sexually dimorphic, showing higher frequency and duration in males respect to females. Moreover, neonatal orchiectomy on postnatal day 2 significantly decreases the incidence of SWDs, whereas adult orchiectomy significantly increases SWDs frequency. These findings suggest that androgens may differentially modulate absence-like seizures depending on the developmental stage. The aim of this study was to evaluate the effects of subcutaneous testosterone propionate administration at doses of 2, 4, and 8 mg/Kg on the frequency and total duration of spike-wave discharges in adult male taiep rats. Adult orchiectomized male *taiep* rats were implanted with cortical EEG electrodes and assigned to four experimental groups: vehicle or testosterone propionate (TP; 2, 4, or 8 mg/Kg, s.c.). TP was dissolved in extra virgin olive oil. Two 24-hour EEG recordings per rat were obtained. SWD were visually identified by abrupt onset and offset, spike-wave morphology, and rhythmic activity. Frequency and total duration were quantified across 24 h and compared respect to subjects with oil administration. Testosterone propionate administration significantly decreased the total number of SWDs in adult orchiectomized male *taiep* rats compared with their respective control recordings ($F_{(1,4)}$ =

8.58, P = 0.043). This effect was detected at all three doses tested, 2, 4, and 8 mg/Kg, with the greatest reduction observed in the 4 mg/Kg group. These results suggest that TP modulates the thalamo cortical circuit responsible for the generation of absence-like discharges in *taiep* rats. Moreover, these findings are consistent with the reduction of absence seizures observed in humans after puberty, supporting a potential role of androgenic signaling in the modulation of absence epilepsy.

Disclosures: R. Castillo: None. **C. Cortes:** None. **A. Ugarte:** None. **J.R. Eguibar:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

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Program #/Poster #: PSTR259.12/T23

Topic: B.08. Epilepsy

Support: R01NS126594
R01NS131670
RF1NS131762

Title: Generating brain metabolic profiles of blood brain barrier Glut1 KO mice

Authors: *E. PEREYRA[1], G. NAIK[1], M. P. BEENHAKKER[2];
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Abstract: Glucose Transporter Type 1 (GLUT1) Deficiency Syndrome is a rare genetic disorder characterized by a haploinsufficiency in SLC2A1, the gene encoding GLUT1 protein. Patients with GLUT1 Deficiency Syndrome present with seizures that do not respond to anti-seizure medications. The ketogenic diet serves as the only treatment for patients with GLUT1 Deficiency Syndrome. Notably, the exact mechanism accounting for the diet's effectiveness remains unknown. However, the efficacy of the ketogenic diet underscores the promise that metabolic targets can be used to treat GLUT1 Deficiency. Our lab has observed that mice with blood brain barrier (BBB) GLUT1 loss present with a reduction in cerebral spinal fluid concentration and develop severe tonic clonic seizures. Cumulatively, these data suggest that chronic glucose depletion is sufficient to induce seizures in our BBB GLUT1 KO model. However, how brain metabolism is impacted following BBB GLUT1 depletion, and if such metabolic changes drive hyperexcitability, is largely unknown.
To resolve metabolic alterations in our BBB GLUT1 KO model, we seek to establish a comprehensive metabolic profile of brain metabolism prior to and following the onset of seizures. Furthermore, we seek to establish if BBB Glut1 KO mice maintained on the ketogenic diet have a reduction in seizure frequency and severity. Additionally, we aim to resolve the brain metabolic profile of BBB Glut1 KO mice maintained on the ketogenic diet to elucidate how the ketogenic diet impacts brain metabolism in BBB GLUT1 KO mice. We achieve this by using

desorption electrospray ionization (DESI) imaging to generate spatially resolved mass spectra at defined pixels across a whole brain section. Preliminary data indicate that DESI-imaging can resolve regional metabolite levels across a whole brain section. With this approach, we can evaluate brain structure-specific changes in metabolite levels in our BBB GLUT1 KO model. Overall, our study provides a preliminary spatial map of brain metabolic features associated with the development of severe tonic clonic seizures following BBB GLUT1 loss. These data will serve as a stepping stone to (1) identify metabolic changes that potentially drive hyperexcitability, and (2) elucidate metabolic targets that may serve as treatment options to mitigate seizures in patients with GLUT1 Deficiency Syndrome.

Disclosures: E. Pereyra: None. **G. Naik:** None. **M.P. Beenhakker:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.13/T24

Topic: B.08. Epilepsy

Title: EXPRESSION OF c-Src, Cyclin D, AND c-Myc IN THE Wnt/β-catenin PATHWAY IN THE LIMBIC SYSTEM OF RATS SUBJECTED TO CALORIC RESTRICTION WITH KINDLING-INDUCED EPILEPTIC SEIZURES

Authors: *O. VILLA-ROBLEDO[1,5], N. SERRANO[2], C. R. OSORNIO[3], J. PÉREZ VILLAVICENCIO[2], R. PEREZ RUBIO[2], R. OSORNIO[4];
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Abstract: EXPRESSION OF c-Src, Cyclin D, AND c-Myc IN THE Wnt/β-catenin PATHWAY IN THE LIMBIC SYSTEM OF RATS SUBJECTED TO CALORIC RESTRICTION WITH KINDLING-INDUCED EPILEPTIC SEIZURES Omar Villa-Robledo[1,2], Ricardo Perez-Rubio[1,3], Javier Perez-Villavivencio[1,4], Rebeca Jimenez-Hernandez[1,5], Héctor Romo-Parra[6], Ángel Lee[7], Norma Serrano-García[1], *Carmen María Rubio[1]
Caloric restriction (CR) reduces seizure frequency in drug-resistant epilepsy through poorly understood intracellular mechanisms. The Wnt/β-catenin pathway activates C-Src, Cyclin D, and c-Myc — downstream targets implicated in neuroplasticity and excitability — but its modulation by CR in the limbic system is uncharacterized. This exploratory study examined the effect of CR on Wnt/β-catenin downstream signaling in the hippocampus and amygdala of rats with kindling-induced seizures. Adult male Wistar rats (250–300 g; sex differences not assessed) underwent stereotaxic electrode implantation in the basolateral amygdaloid nucleus and received daily

electrical stimulation (60 Hz, 1.0 ms, 400 μA). Four groups were studied (n=8/group): non-intervention control, kindling, CR alone, and kindling+CR; CR consisted of a 20% caloric reduction. Seizure progression was assessed over 21 days by blinded behavioral staging (Racine scale) and electroencephalographic recording. Kindling+CR animals did not reach generalized seizures (stage 4–5) after 21 stimulation days. These findings demonstrate that CR markedly attenuates limbic epileptogenic progression in the kindling model and provide behavioral and electrophysiological evidence supporting Wnt/β-catenin pathway modulation as a candidate mechanism, with translational implications for drug-resistant epilepsy.

Disclosures: O. Villa-Robledo: None. **N. Serrano:** None. **C.R. Osornio:** None. **J. Pérez Villavicencio:** None. **R. Perez Rubio:** None. **R. Osornio:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.14/T25

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

Support: NIH/NINDS R01 NS073768
Seed Grant from the American Epilepsy Society/NORSE Institute
National Research Foundation of Korea, NRF- 2022R1A2C1007320
Child Health Research Institute Grant, UNMC

Title: Colostrum-Extracellular Vesicles for New-Onset Refractory Status Epilepticus

Authors: *H.-Y. SHEN[1], S. SIL[2], N. FERRIS[1], G. SCHAVEE[1], M. KUMAR[2], S. AKTER[2], G. HU[2], H. E. GENDELMAN[2], S. KOH[1,3];
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Abstract: New-onset refractory status epilepticus (NORSE) is life-threatening medical emergency where seizures continue despite best in practice anti-seizure medications. The sequalae is a high mortality and severe long-term neurological disability. Emerging evidence suggests that immune dysfunction and neuroinflammation drive NORSE. We posited that extracellular vesicles (EVs) can combat NORSE through immune modulation, neuroprotection, and BBB penetrance. However, the use of EVs has been limited due to their production, rapid clearance, immune reactivity, drug loading, and lack of standard functional testing. We have overcome each of these using a bovine colostrum material source. Colostrum-derived EVs (C-EVs) are enriched in bioactive proteins and immune regulatory microRNAs and can be safely administered to humans. The C-EV treatment for NORSE was developed. A NORSE model was established by intrahippocampal kainic acid (IHKA, 150 ng) injection in postnatal day 40 (P40) C57BL/6J mice (*n*=45). Daily i.p. injections of C-EVs (*n*=22) or a vehicle control (*n*=23) were

given for 20 days. Seizure burden was assessed by intrahippocampal EEG at 1 and 3 weeks. EV biodistribution was evaluated by IVIS 24 h parallel studies to assess BBB penetrance and distribution. Neuroinflammation was assessed by IBA1, GFAP, and NeuN immunohistochemistry. Peripheral immune responses were evaluated by regulatory T cell (Tregs) quantification and hippocampal cytokine profiling. Results: Seizure Reduction. C-EV significantly reduced seizure frequency at weeks 1 and 3 (p=0.0392 and p=0.0013). Neuroprotection. C-EV-treatment led to increased numbers of NeuN-positive neuronal densities (p=0.0496) and preservation of hippocampal cellular architecture. Neuroinflammation. C-EV reduced glial (microglial and astrocyte) activation (IBA1 expression, p=0.0104) and the latter in the CA1 (28% reduction) and CA3 hippocampal regions (22% reduction; p=0.0317). Brain delivery and biodistribution. IVIS affirmed C-EV BBB penetrance with hippocampal accumulation approximately 7.6-fold higher in IHKA-treated mice compared with sham controls. Immune Modulation: C-EV-treated mice increased numbers of circulating Treg (p=0.0268) and demonstrated reduced hippocampal pro-inflammatory cytokines including IL-1β (2.2-fold reduction), IL-6 (3-fold reduction), and TNF-α (1.7-fold reduction). C-EV treatment was safe and well-tolerated in P40 mice. Together, C-EV reduced seizure burden, suppressed glial activation, preserved neuronal integrity in safely in preclinical murine model of NORSE. These findings support the development of C-EVs as a novel therapeutic agent for NORSE.

Disclosures: H. Shen: None. **S. Sil:** None. **N. Ferris:** None. **G. Schavee:** None. **M. Kumar:** None. **S. Akter:** None. **G. Hu:** None. **H.E. Gendelman:** None. **S. Koh:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.15/T26

Topic: B.08. Epilepsy

Support: NS096234 (ALB)

Title: Differential behavioral, reproductive, and immune outcomes after status epilepticus in male and female rats

Authors: *N. PINZON[1], Y. LI[2], A. L. BREWSTER[1];
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Abstract: Epidemiological studies reveal sex differences in epilepsy incidence, clinical presentation, and treatment outcomes. Males exhibit higher overall epilepsy incidence and greater susceptibility to injury-related epilepsy, whereas females more frequently present with idiopathic generalized epilepsy and have more adverse effects from anti-seizure drugs. Recent transcriptomic and proteomic studies suggest that distinct sex-specific molecular pathways may contribute to the development and maintenance of epileptic networks. However, the impact of

these differences on epileptogenesis remains unclear. Therefore, this study investigated sex-specific behavioral and immune responses following SE in adult rats. SE was induced in adult male and female Sprague Dawley rats with pilocarpine (280 mg/kg, i.p.) and interrupted after 1 h with diazepam (10 mg/kg, i.p.)(n = 10/group). Controls received saline. We recorded daily body weight and estrous cycle stages and video-monitored behavioral seizure activity from days 1-21 after SE. At 3 weeks post SE, we used the open-field (OF) test to assess locomotion and anxiety-like behaviors. Next, hippocampi were collected to assess levels of various cytokines, complement C3 activation, and gliosis through immunoassays. Although all SE-treated rats lost weight right after SE, males returned to control weight levels by 3 weeks, while females regained weight by day 4 and later surpassed control weights. SE females showed a disrupted estrus cycle, with changes in the length of different cycle stages. All rats with SE experienced spontaneous tonic-clonic seizures, confirming epilepsy development. In the OF test, SE females showed increased locomotion compared to controls ($p<0.05$). Locomotion was not altered in SE males. In contrast, SE males spent more time in the center of the OF arena ($p<0.05$) compared to male controls, suggesting altered anxiety-like behaviors. Cytokine analysis revealed lower levels of GM-CSF, IFN-γ, IL-2, IL-5, IL-10, and TNF-α in the hippocampus of both males and females with SE compared with their respective controls ($p<0.05$). SE triggered hippocampal gliosis and complement activation in all rats. These findings demonstrate that SE induces sex-specific alterations in metabolism (weight changes), anxiety-like behaviors, and the reproductive cycle in females. While both sexes exhibited reduced cytokine levels and increased C3 levels in response to SE, divergent profiles of cytokine correlations were observed across all groups. Therefore, additional analyses are required to determine whether the immune responses are sex- and hormone-dependent in the context of SE.

Disclosures: N. Pinzon: None. **Y. Li:** None. **A.L. Brewster:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.16/T27

Topic: B.08. Epilepsy

Support: NS096234 (ALB)
Children's Brain Diseases Foundation (ALB)

Title: Determining the role of TREM2 in seizure activity and inflammation during status epilepticus

Authors: *Z. SADRI[1], Y. LI[2], A. L. BREWSTER[1];
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Abstract: Microglia are essential for brain health and disease response. In a healthy brain, they constantly monitor the parenchyma, allowing quick inflammatory and phagocytic responses to immune challenges and disruptions. During seizures, microglia adopt reactive phenotypes characterized by altered surveillance, inflammation, and phagocytosis. The microglial receptor TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) can regulate survival, inflammation, and phagocytosis, but its role in epilepsy remains unclear. This study investigates how TREM2 loss affects neural activity and inflammation following status epilepticus (SE). To test this, we used the pilocarpine-induced SE mouse model of acquired epilepsy and examined behavioral and electrographic seizures along with hippocampal cytokine levels. Adult TREM2KO and C57BL/6J (WT) mice were implanted with cortical electrodes, and video-EEG was recorded. The Racine scale was used to score behavioral seizures. To induce SE, mice received pilocarpine (300 mg/kg, i.p.) or saline (controls). Groups included males (M) and females (F): WT controls (C), WT-SE, TREM2 KO-C, and TREM2 KO-SE, n = 7/group. After one hour of SE, mice were transcardially perfused with saline, and hippocampi were collected for histological and biochemical analyses. EEG traces were analyzed for seizure onset time, duration, severity, and total spectral power (0-70 Hz). Neuronal activation was evaluated using P-S6 immunoreactivity, an mTOR marker, while ELISAs quantified the inflammatory cytokines IL-6, TNF-α, and IL-1β. Comparisons of EEG analyses of SE groups by sex and genotype revealed that TREM2 KO mice exhibited higher spike frequency and maximum peak power within the first 15 minutes after pilocarpine injection compared to WT mice, suggesting a lower seizure threshold. Despite these early differences, no significant effects of sex or genotype were observed in electrographic epileptiform activity or total spectral power (0-70 Hz) across the entire SE episode ($p > 0.05$, ANOVA). Robust P-S6 immunoreactivity in all SE groups relative to controls indicated neuronal activation. Higher IL-6 levels were found in male WT-SE mice compared to WT-C males ($p < 0.05$), whereas IL-6 levels did not increase in TREM2 KO-SE males relative to TREM2 KO controls. TNFα and IL-1β levels were not different across groups. Overall, these results indicate that loss of TREM2 increases neuronal excitability following pilocarpine treatment in both male and female mice. In addition, TREM2 appears to modulate seizure-induced IL-6 responses specifically in males, suggesting a sex-dependent effect that warrants further investigation.

Disclosures: Z. Sadri: None. **Y. Li:** None. **A.L. Brewster:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.17/T28

Topic: A.06. Developmental Disorders

Title: Integrated Behavioural and NMDA-induced Seizure Phenotyping in a Mouse Model of CDKL5 Deficiency Disorder

Authors: *D. SELLERI[1], E. PASCHEN[2], C. J. MALTBY[2], M. PALMAS[2], A. MOREIRA DE SA[2], J. PINTO[2], M. BIANCHI[2];
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Abstract: Background: CDKL5 Deficiency Disorder (CDD) is a rare developmental and epileptic encephalopathy characterised by early-onset refractory seizures, profound intellectual disability, and limited motor function. Comprehensive preclinical characterisation combining sex-stratified behavioural profiling with neuroanatomical and molecular endpoints, alongside seizure susceptibility and pharmacological validation, has to date remained unavailable as an integrated platform for testing novel molecules in CDD. **Methods**: Male *Cdkl5*-knockout (KO) and female *Cdkl5*-heterozygous (Het) mice from the *B6.129(FVB)-Cdkl5^tm1.1Joez^/J* line were characterised at 4 and 10 weeks across eight assays: limb clasping, burrowing, open field, elevated zero maze, marble burying, Y-maze, reciprocal social interaction, and nest building. Brain hemispheres were used for Golgi-Cox staining and western blot quantification of CDKL5 protein and phosphorylated End Binding Protein 2 (pEB2), a direct readout of CDKL5 kinase activity. In an independent cohort, an NMDA dose-response study (60, 80, and 100 mg/kg, i.p.) was conducted in adult Cdkl5-KO versus WT mice, followed by fenfluramine efficacy testing at a selected dose. **Results**: *Cdkl5*-KO males showed robust deficits across all tests; Het females showed a milder but consistent phenotype reflecting mosaic X-inactivation. Longitudinally, elevated zero maze worsened; limb clasping, open field, marble burying, and nest building were stable; burrowing and Y-maze were rescued. Golgi-Cox staining provided morphological correlates across genotypes. CDKL5 and pEB2 were significantly reduced in KO and Het versus WT, confirming pathway dysfunction. The NMDA dose-response identified for the first time the dose at which *Cdkl5*-KO mice seize while WT remain unaffected, establishing a genotype-selective pharmacological window. Fenfluramine showed antiseizure efficacy within this window. **Conclusions:** These studies establish a multi-modal preclinical platform encompassing behavioural, neuroanatomical, molecular biomarker, and seizure susceptibility readouts. Fenfluramine efficacy within the genotype-selective NMDA paradigm provides a clinically anchored benchmark for novel small molecule candidates, positioning this platform to support therapeutic development in the DEE space.

Disclosures: D. Selleri: None. **E. Paschen:** None. **C.J. Maltby:** None. **M. Palmas:** None. **A. Moreira de Sa:** None. **J. Pinto:** None. **M. Bianchi:** None.

Poster

PSTR259: Epilepsy Animal Models: Comorbidity, Neuroinflammation, Metabolism, and Neuroprotection

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR259.18/T29

Topic: A.06. Developmental Disorders

Support: NIH R01 NS083373
NIH R01 NS037402
NIH R01 GM077875

Title: Relationship between KCTD7 loss and Progressive Myoclonic Epilepsy type 3 (PME3): A preclinical evaluation of mechanism and pathophysiology.

Authors: *V. O. OMONIYI[1], K. METZ[2], M. KULKARNI[3], H. LAMB[4], R. SOMAN[5], A. SAITO[6], A. KAMIYA[9], S. ROBINSON[7], L. L. JANTZIE[8], J. HARDWICK[4];
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Abstract: Biallelic mutations in the *KCTD7* gene result in the rare neurodevelopmental-neurodegenerative disorder, progressive myoclonic epilepsy type III (PME3), characterized by early onset intractable myoclonic seizures, developmental delay and regression, cognitive and motor deficits. Our studies of patient fibroblasts and brain tissue provide evidence for an underlying autophagy-lysosome pathway defect. In further support, we found that yeast Whi2, which shares sequence similarity to human KCTD7, is a new inhibitor of yeast TORC1 activity by binding yeast Tor1 kinase, and yeast lacking a functional *WHI2* gene have sustained TORC1 activity and reduced autophagy. To investigate the cellular and molecular mechanisms of PME3, we developed a *Kctd7* knockout mouse model and are currently investigating a role for mTORC1, which is hyperactivated in several other epilepsies and autophagy disorders. We hypothesize that KCTD7 may also regulate mTORC1, potentially facilitating epileptogenesis. Using a *Kctd7* promoter-driven β-gal reporter mouse, we identified spatiotemporal expression of *Kctd7* in neurons of brain regions associated with neuronal hyperexcitability, executive function, and sensory motor performance. Interestingly, *Kctd7* KO mice have a highly penetrant audiogenic seizure phenotype not observed in heterozygous or WT littermates (n=4 independent experiments, before and after refreshing the colony, each test with 2-6 male and female mice per genotype, ages 1-11 months, $p<0.0001$, unpaired 2-tailed T test). To induce seizures, mice were exposed to four 60-second pulses from a commercial personal alarm device with 2 min rests between pulses Similar to neuroimaging findings in PME3 patients at advanced stages of disease, preliminary results from structural and diffusion tensor magnetic resonance imaging in mice suggest that *Kctd7* knockout mice have diffuse cerebral abnormalities on MRI, including ventriculomegaly, cortical atrophy, and periventricular white matter changes, including encephalomalacia. Western blot analyses of brain and mouse embryo fibroblasts (MEFs) to assess mTORC1 kinase function activation were inconclusive thus far. However, more sensitive immunohistochemical labeling showed an increase in phospho-S6 in the deeper layer of the cortex in *Kctd7* knockout mice (n=2 KO, n=3 WT/Het). Seizure phenotypes and MRI findings in mice are consistent with clinical features of PME3 patients, suggesting that our *Kctd7* knockout mouse will serve as an excellent PME3 model for testing potential therapeutics, especially given that *Kctd7* knockout mice exhibit a strong seizure phenotype at the earliest age tested (1 month).

Disclosures: V.O. Omoniyi: None. **K. Metz:** None. **M. Kulkarni:** None. **H. Lamb:** None. **R. Soman:** None. **A. Saito:** None. **A. Kamiya:** None. **S. Robinson:** None. **L.L. Jantzie:** None. **J. Hardwick:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.01/T30

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

Support: NIAAA Grant R01AA027768
NIAAA Grant U01AA025932
NIAAA Grant R01AA030293

Title: Striatal Hyperactivity Strengthens D1-Striatal Inhibition of Basal Forebrain Cholinergic Neurons in an Alzheimer's Disease Model

Authors: *X. XIE[1], Y. HUANG[2], Z. LI[3], J. WANG[4];
[1]Texas A&M Hlth. Sci. Ctr., Bryan, TX; [2]Texas A&M Inst. for Neurosci., College Station, TX; [3]Neurosci., Texas A&M Univ., College Station, TX; [4]Dept. of Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Univ. Sci. Ctr., Bryan, TX

Abstract: Basal forebrain cholinergic projection neurons (CPNs) are essential for cognitive function and are particularly vulnerable in Alzheimer's disease (AD). However, the upstream circuit mechanisms that suppress CPN activity in AD remain poorly understood. Here, we tested whether inhibitory striatal input to CPNs is altered in the 5xFAD mouse model of AD. Using trans-synaptic tracing, confocal imaging, optogenetics, pharmacology, and whole-cell patch-clamp recordings, we mapped striatal-basal forebrain connectivity and examined AD-associated changes in this circuit. Trans-synaptic tracing identified basal forebrain neurons, including CPNs, that receive striatal input. Optogenetic stimulation revealed that dopamine D1 receptor-expressing striatal neurons evoked robust GABAA receptor-mediated inhibitory postsynaptic currents in CPNs, whereas D2/A2A-expressing inputs produced comparatively weak responses. D1-striatal inputs preferentially targeted CPNs over neighboring non-CPNs and showed evidence of monosynaptic connectivity. In 5xFAD mice, D1-expressing striatal neurons displayed enhanced excitatory synaptic drive, larger AMPAR- and NMDAR-mediated responses, and increased current-evoked firing. In parallel, CPNs from 5xFAD mice exhibited reduced basal firing, increased spontaneous inhibitory synaptic input, larger evoked inhibitory responses, and a lower paired-pulse ratio, consistent with elevated presynaptic GABA release onto CPNs. Direct optogenetic stimulation of D1-striatal axons further confirmed stronger inhibitory responses in CPNs from 5xFAD mice than in controls. Together, these findings identify a preferential D1-striatal inhibitory projection to basal forebrain CPNs that is strengthened in 5xFAD mice. This circuit alteration may contribute to cholinergic hypofunction and cognitive impairment in AD.

Disclosures: X. Xie: None. **Y. Huang:** None. **Z. Li:** None. **J. Wang:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.02/T31

Topic:

Support: R01AA027768
U01AA025932
R01AA030293

Title: Astrocyte-Associated Tau Spread in an Alzheimer's Disease-Vulnerable vHPC-PFC Circuit

Authors: *Z. LI[1], R. KAYED[2], J. WANG[3];
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Abstract: Alzheimer's disease (AD) is characterized by progressive tau pathology and circuit dysfunction. Excessive alcohol use is a modifiable risk factor for dementia, but whether alcohol accelerates tau propagation through defined AD-relevant circuits remains unclear. We focused on the ventral hippocampus (vHPC)-prefrontal cortex (PFC) pathway, a circuit important for cognition and emotional regulation that is vulnerable in AD and sensitive to alcohol-related hyperactivity. As an initial step toward defining how tau spreads through this pathway, we bilaterally injected rAAV-CAG-tau(hP301L)-EGFP into the vHPC of wild-type and PS19 mice and evaluated tau expression and propagation using GFP fluorescence, AT8 phospho-tau staining, and AT13 total tau staining. In wild-type mice, AAV-tau produced robust local expression at the vHPC injection site and GFP/tau-positive labeling in downstream regions, including the entorhinal cortex, basal forebrain, and prefrontal targets. Within the PFC, labeling was detected mainly in fibers, with limited somatic labeling. In contrast, PS19 mice showed GFP-positive cell bodies in the PFC after the same vHPC injection, suggesting that a tau-vulnerable background facilitates distal spread or uptake of tau-associated signals. We also observed GFP-expressing astrocyte-like cells in the PFC, raising the possibility that tau released from cortical terminals is taken up by astrocytes in downstream cortex. To test whether alcohol further enhances tau propagation, we have established a chronic intermittent alcohol drinking paradigm and are incorporating human-derived tau preformed fibrils into this circuit-mapping strategy. In parallel, we are developing an AAV-based tau-targeted chimeric antigen receptor astrocyte (CAR-A) approach to determine whether astrocyte-directed tau clearance can limit extracellular tau spread. Together, these preliminary findings identify a vulnerable hippocampal-prefrontal pathway for tau propagation, support a potential astrocyte-associated mechanism of spread, and establish a platform for testing alcohol as an accelerator of AD-related tau pathology and CAR-A therapy as an intervention.

Disclosures: Z. Li: None. **R. Kayed:** None. **J. Wang:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.03/T32

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

Support: NIH Grant MH113257

Title: Spatial and age dependent analysis of choline acetyltransferase (ChAT) expression in cerebellar basket cells of rhesus macaque

Authors: *M. ELLIOTT[1], K. S. ROCKLAND[3], C. J. ZEISS[2], Z. KRSNIK[4], P. RAKIC[1], A. DUQUE[1];
[1]Neurosci., [2]Comparative Med., Yale Univ. Sch. of Med., New Haven, CT; [3]Anat. and Neurobio., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA; [4]Sch. of Med. Univ. of Zagreb, Zagreb, Croatia

Abstract: Except for our previous report (IBRO 2023), cerebellar cholinergic basket cells (BCs), identified by the expression of the synthesizing enzyme choline acetyltransferase (ChAT), have not previously been investigated because they were not previously observed. Since their discovery in the elderly rhesus macaque, the presence of ChAT+ BCs has been corroborated by the PI and colleagues in elderly mouse, rat, and human. Changes in the cholinergic system are known to be involved in elderly cognitive deterioration and very prominent in Alzheimer's disease (AD). It is suspected that if cholinergic changes are occurring and can become so noticeable in the cerebellar cortex, which is classically a structure not associated with the presence of cholinergic cells, then changes in known cholinergic areas such as the basal forebrain are very likely occurring and deserve concomitant attention. Using the extensive Collection 6 of the MacBrain Resource Center (MBRC) database we are systematically investigating the expression of ChAT in the rhesus macaque cerebellum. Preliminary data includes n=37 animals ranging in age from 93 embryonic days (E) to 32 years old. The data most notably shows age-dependent presence of ChAT+ BCs that form a perisomatic basket around Purkinje cells and a "pinceau" plexus around axon initial segments (AISs) that becomes evident in older animals (~10 years or older). We also detected ChAT+ neuron staining in the vermis of embryonic brains, which seem to disappear shortly after birth. Our preliminary data indicates that, in general, the presence of ChAT+ BCs is higher in rostral as compared to caudal and higher in ventral than in dorsal locations. These findings are of interest in the context of lifespan changes in brain organization that include neurotransmitter switching and may have profound consequences in late life occurring motor and cognitive diseases.

Disclosures: M. Elliott: None. **K.S. Rockland:** None. **C.J. Zeiss:** None. **Z. Krsnik:** None. **P. Rakic:** None. **A. Duque:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.04/U1

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

Support: NIH grant 5R01AG066489

Title: The effect of increasing O-GlcNAc on in vivo CA1 pyramidal cell excitability in wild type and TgF344-AD rats

Authors: *C. G. PERK[1], M. L. GARCIA[1], L. L. MCMAHON[2];
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Abstract: GlcNAcylation is a dynamic post-translational modification involving addition of β-N-acetylglucosamine (GlcNAc) to serine/threonine residues on nuclear and cytosolic proteins. O-GlcNAc transferase adds O-GlcNAc to substrates and O-GlcNAcase (OGA) removes it. O-GlcNAcylation has gained recent attention in Alzheimer's disease (AD), as it competes with serine phosphorylation on tau, where it can decrease hyperphosphorylated tau in transgenic mice and improve memory. Our laboratory and others have previously reported that pharmacologically induced increases in O-GlcNAcylation can dampen intrinsic excitability of CA1 pyramidal neurons recorded in hippocampal slices and induce LTD at CA3-CA1 synapses which requires GluA2-containing AMPAR internalization. Increased O-GlcNAc also decreases the amplitude of voltage-gated Na+ currents, increases the amplitude of voltage-gated K+ currents, and depresses epileptic activity. At the circuit level *in vivo*, no data exist linking the *in vitro* effects of heightened O-GlcNAcylation to altered network activity, and whether this is altered in AD. We recorded CA1 pyramidal cell excitability before and after pharmacologically increasing O-GlcNAc using the OGA inhibitor Thiamet-G (TMG) in 7-8 month old TgF344-AD rats (TG), a rat model of AD, and wild type (WT) littermates, under isoflurane anesthesia. Baseline recordings (5 min) were followed by infusion of ACSF or ACSF + TMG (5 µl infusion of 50-100µM at 0.5 µl/min) in the lateral ventricle and recordings continued for 45 mins. At the end of the recording, brains were harvested for post hoc electrode placement and an increase in O-GlcNAc levels. Individual spike trains were isolated offline before mean firing rate (FR) and coefficient of variation (CV) were calculated for each cell. Recordings from 12 animals yielded 79 neurons (TG ACSF, n = 16, TG TMG, n = 24, WT ACSF, n = 20, WT TMG, n = 19, 3 animals per group). Examining baseline activity revealed no between-strain difference in FR (TG, 4.67 ± 3.44 Hz, n = 40, WT, 5.33 ± 5.08, Hz, n = 39, p = 0.5052) but found CV was lower in TG animals (TG, 1.22 ± 0.27, WT, 1.33 ± 0.18, p = 0.0320), indicating a slightly increased tonic CA1 discharge pattern. No infusion effect on FR (p = 0.8825), a treatment group difference (p = 0.2497), or an infusion x group interaction (p = 0.3768) was detected. CV also showed no infusion effect (p = 0.4130), group difference (p = 0.0730) or a significant interaction (p = 0.1820). These results show altered CA1 firing activity in TG vs WT rats. We are currently

exploring whether higher TMG concentrations are required to depress CA1 firing and how O-GlcNAc might elicit neuron-specific changes in activity.

Disclosures: C.G. Perk: None. **M.L. Garcia:** None. **L.L. McMahon:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.05/U2

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

Support: NIA R03AG100774
Marquette University Way Klingler Science Fellowship

Title: Longitudinal miniscope imaging of prefrontal cortex during working memory in a rat model of Alzheimer’s disease

Authors: L. METKO, C. SCHLUT, G. SCHAMBER, N. VOSHELL, I. A. SAVTCHOUK, R. C. TWINING, *M. R. GILMARTIN;
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Abstract: Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. While amyloid-targeting treatments show promise, their effectiveness is limited to early disease stages, highlighting the need for biomarkers that can predict cognitive decline prior to overt symptoms. Here, we investigated neural activity in the prefrontal cortex as a potential biomarker of early AD using the TgF344-AD rat model, which exhibits progressive amyloid-beta pathology and cognitive impairment. Mixed-sex cohorts of TgF344-AD rats (n = 19) and wildtype controls (n = 20) were trained in the prefrontal-dependent Trial-Unique-Nonmatch-to-Location (TUNL) touchscreen task, assessing working memory across variable delays and spatial separations. Amyloid-beta plaque deposition was tracked longitudinally using post-mortem immunohistochemistry in naïve rats (n=4/genotype/age timepoint) and in vivo two-photon imaging in a subset of trained rats (n=4/genotype, longitudinal). Prelimbic neurons in this subset of trained rats were transfected with GCaMP8f and a GRIN lens was implanted in PL for in vivo miniscope calcium imaging during TUNL testing at multiple age/pathology timepoints. Preliminary results show that amyloid beta accumulation in the hippocampus and medial prefrontal cortex begins around 6 months and progressively increases over months, with hippocampal pathology outpacing prefrontal cortex. Genotype differences in task-related prefrontal activity are evident at 6 months of age before behavioral deficits emerge.

Disclosures: L. Metko: None. **C. Schlut:** None. **G. Schamber:** None. **N. Voshell:** None. **I.A. Savtchouk:** None. **R.C. Twining:** None. **M.R. Gilmartin:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.06/U3

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

Support: R01AA027768
U01AA025932
R01AA030293

Title: Reciprocal feedback loop between Microglia activation and cholinergic neuron activity

Authors: *R. WANG;
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Abstract: Title: Reciprocal feedback loop between Microglia activation and cholinergic neuronactivityAuthor: Runmin Wang[1], Yufei Huang[1,2], Ruifeng Chen[1,3],Ziyi Li[1,2], Xuehua Wang[1] and JunWang[1,2,3]***Affiliation:**1. Department of Neuroscience and Experimental Therapeutics, College of Medicine,Texas A&M University Health Science Center, Bryan, TX 77807, USA;2. Institute for Neuroscience, Texas A&M University, College Station, TX 77843,USA3. Interdisciplinary Faculty of Toxicology, College of Veterinary Medicine andBiomedical Sciences, Texas A&M University, College Station, TX 77843, USA;**Abstract:** Cholinergic signaling is essential for cognitive function, yet how it interacts with brainimmune activity remains unclear. Here, we identify a bidirectional regulatory loop betweenmicroglia and cholinergic neurons in the dorsomedial striatum (DMS). Reduced cholinergicactivity impaired novel object recognition without altering general locomotor activity, suggestinga specific cognitive deficit rather than motor impairment. Loss of cholinergic tone wasaccompanied by increased CD68-positive microglial activation in the DMS, while nocomparable change was observed in the medial prefrontal cortex, indicating a region-specificneuroimmune response. Conversely, microglial activation altered cholinergic neuron physiologyby suppressing spontaneous firing while enhancing intrinsic excitability and inhibitory synapticinput. These findings suggest that cholinergic neurons normally restrain microglial reactivity,whereas activated microglia can feed back to remodel cholinergic neuronal function. Together,our results reveal reciprocal microglia-cholinergic feedback loop in the DMS, in which disruptedcholinergic signaling promotes microglial activation and contributes to impaired noveltyrecognition. This interaction may represent an important neuroimmune mechanism underlyingstriatal cognitive dysfunction.

Disclosures: R. Wang: None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.07/Web Only

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

Title: Rich Club Connectivity Buffers Against ATN Pathology: A Progressive Resilience Gradient Across the Alzheimer's Disease Continuum

Authors: *M. H. PARRISH[1,2], M. H. HUBER[1,2], A. JIANG[1,2], S. SEN[1,2], L. BONILHA[1,2]; [1]Neurol., Univ. of South Carolina Floyd Sch. of Med., Columbia, SC; [2]Div. of Neurol., Prisma Hlth., Columbia, SC

Abstract: Introduction: Rich club connectivity, the tendency of highly connected brain hub regions to be densely interconnected, has been proposed as a marker of neural resilience. While ATN biomarkers (amyloid, tau, neurodegeneration) each independently predict cognitive decline in Alzheimer's disease, whether rich club connectivity moderates these relationships across the full ATN continuum remains unknown. We hypothesized that rich club connectivity would buffer the negative cognitive effects of ATN pathology, with buffering capacity varying as a function of pathological stage. **Methods:** 244 older adults (mean age = 72.75 years, SD = 8.46; 59.4% female; mean MMSE = 27.68, SD = 3.17) underwent amyloid PET (centiloids), tau PET (meta-temporal standardized uptake value ratio; SUVR), structural MRI (bilateral hippocampal volume), and cognitive assessment (Mini-Mental State Examination; MMSE). Rich club connectivity (k=25) was derived from diffusion tractography. Three moderation analyses (PROCESS Model 1, Hayes, 2022; 5,000 bias-corrected bootstrap samples) examined whether rich club connectivity moderated the association between each ATN biomarker and MMSE, controlling for age, sex, race, and ethnicity, with all variables mean-centered prior to analysis. **Results:** Greater amyloid burden, tau burden, and hippocampal atrophy each independently predicted worse MMSE (all *p*s < .001). Rich club connectivity significantly moderated all three relationships (all interaction *p*s < .001), with the moderation interactions independently accounting for an additional 10.2%, 5.9%, and 7.0% of variance in MMSE for amyloid, tau, and hippocampal volume respectively. A progressive buffering gradient emerged across the ATN continuum: the negative effect of amyloid on cognition was fully attenuated at high rich club connectivity, with Johnson-Neyman analysis indicating this threshold was exceeded by 28.3% of the sample. Tau pathology required greater connectivity for full buffering, exceeded by only 19.3% of the sample. Hippocampal atrophy required the highest connectivity threshold of all, present in only 6.6% of the sample. **Conclusions:** Rich club connectivity confers cognitive resilience across the ATN continuum, with progressively greater network integrity required to buffer increasingly downstream pathological processes. These findings suggest rich club connectivity may represent a tractable neural substrate of cognitive reserve, and that preserving hub network integrity could be a meaningful target for maintaining cognitive function in the face of Alzheimer's disease pathology.

Disclosures: M.H. Parrish: None. **M.H. Huber:** None. **A. Jiang:** None. **S. Sen:** None. **L. Bonilha:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.08/U4

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

Support: NIH Intramural Research Program Z01 ES090089

Title: Cholinergic regulation of GABA release onto MS/DBB cholinergic neurons is disrupted in 5XFAD mice

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Abstract: Cholinergic input from the medial septum/diagonal band of Broca (MS/DBB) to the hippocampus has been shown to be critical for learning and memory. Disruption of this cholinergic pathway, as occurs in Alzheimer's disease (AD), can lead to significant memory impairments. Within the MS/DBB, cholinergic neurons synapse onto local GABAergic neurons, activating muscarinic acetylcholine receptors (mAChRs) and subsequently increasing GABA release back onto cholinergic neurons. It is possible that this feedback circuit may be critical for regulating activity during periods of elevated or rhythmic firing, which are critical for memory encoding and retrieval and are disrupted in AD. Despite the importance of cholinergic and GABAergic interactions in the MS/DBB, there is little known about how inhibitory synaptic transmission onto cholinergic neurons in the MS/DBB is altered by pathological exposure to amyloid-β. In order to address this question, we crossed ChAT-Cre mice to 5XFAD mice and injected Cre-dependent AAV containing ChR2/mCherry into the MS/DBB of 6-, 9-, and 12-month-old male and female offspring. This allowed us to specifically label cholinergic neurons in a mouse model of AD. We then performed whole-cell voltage clamp recordings from ChAT+ neurons in the MS/DBB in acute slices 2-3 weeks after injection. We recorded spontaneous inhibitory postsynaptic currents (sIPSCs) prior to and following bath application of the acetylcholine agonist carbachol (50 μM). We found that baseline sIPSC frequency onto MS/DBB cholinergic neurons is lower in 9-month-old 5XFAD females compared to WT, and baseline sIPSC amplitude is lower in 12-month-old 5XFAD males. Bath application of carbachol significantly increased sIPSC frequency onto cholinergic neurons in WT male and female mice in all ages studied. Conversely, in 5XFAD mice, there was no significant effect of carbachol on sIPSC frequency at any age in either males or females. Significant differences in the percent change in sIPSC frequency induced by carbachol in WT and 5XFAD mice were seen in 6- and 9-month-old females and 9-month-old males. Bath application of the M1 mAChR antagonist pirenzepine (10 μM) blocked the effects of carbachol in WT mice. Together, these results suggest that in 5XFAD mice, there are transient changes in spontaneous GABA release onto cholinergic neurons in the MS/DBB, and there is a loss of M1 receptor-mediated regulation of GABA release. These changes in inhibitory input onto cholinergic neurons may impact cholinergic signaling both in the MS/DBB and in the hippocampus, which may contribute to deficits in cognition.

Disclosures: J.C. Damborsky: None. **J.L. Yakel:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.09/U5

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

Support: 5R01NS105691-07
5R01NS129632-03

Title: Dynamic relationship of cortical amyloid plaque burden and electrophysiological activity in aged APP/PS1 mice

Authors: ***T. THAI**[1], C. GARCIA PADILLA[1], N. SUEMATSU[2], T. D. KOZAI[1];
[1]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [2]Kyoto Sangyo Univ., Pittsburgh, PA

Abstract: Alzheimer's disease (AD) is a neurodegenerative condition characterized by progressive amyloid-beta plaque burden and disruptions in neural circuit function. Although amyloid pathology has been associated with altered synaptic transmission and inhibitory signaling, most evidence comes from endpoint histological studies. As a result, the temporal relationship between plaque progression and circuit dysfunction remains unclear, particularly at late disease stages. To address this gap, we tested whether plaque accumulation and neuronal activity follow similar temporal trajectories. In this study, we combined repeated widefield imaging of methoxy-X04-labeled cortical plaques with in vivo electrophysiology in 17 to 19-month-old APP/PS1 and wild-type (WT) mice over 7 weeks post-implant. Temporal phases were defined as: acute (week 1), intermediate (weeks 2-4), and chronic (weeks 5-7). Plaque count per mm2 did not differ between acute (15.665 ± 0.888, n=11 imaging sessions), intermediate (13.623 ± 1.516, n=7 imaging sessions), and chronic phases (13.252 ± 0.826, n=9 imaging sessions), suggesting that the implant did not alter late-stage plaque load (GLMM, $F(2,24)=0.665$, $p=0.523$). As neuronal hyperactivity is common in AD, we compared the spontaneous firing rate (FR) between APP/PS1 and WT control mice. During a 5-minute electrophysiological recording, the spontaneous FR was significantly lower in APP/PS1 mice in the acute phase compared to WT controls (N=4 animals/group, Mann-Whitney U, AD: 13.5±1.01Hz vs WT: 20.02±2.54Hz, $p=0.019$), reflecting an early post-implantation effect rather than AD phenotypes. In the following phases, we saw a recovery of spontaneous FR in the intermediate (AD: 14.85±0.80Hz vs WT: 14.57±4.16Hz, $p=0.711$) and chronic phases (AD: 12.86 ± 1.19Hz vs WT: 15.08 ± 3.78Hz, $p=0.904$). Correlating spontaneous FR and plaque count per area revealed a strong positive relationship in the intermediate phase ($R=0.719$, slope=0.364) and a moderate negative relationship in the chronic phase ($R=-0.610$, slope=-0.701). As plaque count per area was stable, the reversal of the slope sign indicates a phase-dependent spatial relationship between plaque burden and neuronal activity, rather than similar temporal trajectories. Altogether, this study reveals a potential spatial relationship between plaque burden and neuronal activity in late stages of AD. Future analyses will assess resting state and visually evoked hemodynamics in APP/PS1 and WT mice to identify deficits in neurovascular coupling associated with plaque accumulation.

Disclosures: T. Thai: None. **C. Garcia Padilla:** None. **N. Suematsu:** None. **T.D. Kozai:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.10/U6

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

Support: NIH R01 AG070831
Howard Hughes Medical Institute
Freedom Together Foundation

Title: Scalable profiling of subcellular pathological states in vulnerable Alzheimer's disease circuits

Authors: *D. LEIBLE[1,2,3], L. LIU[2], E. CALLAHAN[3], A. NGO[2], M. ALAWI[4], Z. KE[2], R. HUNG[1,3], D. WEI[5], E. S. BOYDEN[3], L.-H. TSAI[2];
[1]Dept. of Brain and Cognitive Sci., [2]Picower Inst. for Learning and Memory, [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [4]Xpress AI, Inc., Palo Alto, CA; [5]Computer Sci. Dept., Boston Col., Chestnut Hill, MA

Abstract: Alzheimer’s disease (AD) exhibits a stereotyped progression of amyloid and tau pathology across neural circuits, suggesting that neurodegeneration arises from selective circuit vulnerability. The subiculum (Sub) and its long-range fornix projections to the mammillary bodies (MB) are affected early in disease and have been strongly implicated in AD-associated memory deficits. At the subcellular level, this circuit vulnerability is associated with the development of dystrophic axons, which exhibit profound endolysosomal dysfunction and are thought to promote amyloid plaque formation. However, the factors that confer axon-specific vulnerability and drive the emergence of dystrophic pathology remain poorly understood. To better understand how amyloid pathology progresses along circuits, we investigated anatomical, molecular, and activity-dependent determinants of vulnerability within the Sub-MB circuit. Anterograde tracing in 3-6-month-old, male 5xFAD and APP knock-in mice revealed pronounced projection-specific susceptibility: medial MB-targeting axons develop abundant lysosome-filled dystrophies, whereas neighboring lateral projections are largely spared. Single-nucleus RNA sequencing of projection-defined neurons demonstrated coordinated upregulation of cholesterol biosynthesis pathways within vulnerable populations, implicating altered lipid homeostasis and axo-myelin metabolic interactions as a potential determinant of selective vulnerability. Electrophysiological recordings further revealed circuit hyperactivity, consistent with the presence of early functional alterations in neuronal signal propagation within vulnerable projection populations. To determine how amyloid accumulation, lysosomal dysfunction, and axo-myelin abnormalities converge within individual axons to shape early pathological progression, we developed a scalable Expansion Microscopy-based platform for population-scale single-axon analysis. By integrating structural pan-protein staining, viral tagging of circuit-

defined subpopulations, and multiplexed antibody labeling for high-dimensional molecular readout, this approach enables quantitative mapping of early amyloid pathology within its molecular and subcellular context. Preliminary analyses reveal diverse axonal pathological states, including spatially continuous amyloid accumulations at the axo-glial interface, localized axonal swelling, and diffuse extracellular amyloid deposition between neighboring axons.

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Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.11/U7

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

Support: AARF-22-970734

Title: Altered IGF1 signaling in inhibitory microcircuits in Alzheimer’s disease

Authors: *A. SANTI[1], R. MONGA[2], K. KUCHIBHOTLA[3];
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Abstract: Insulin-like growth factor 1 (IGF1) is a neurotrophic hormone implicated in Alzheimer’s disease (AD) and age-related cognitive decline. While largely produced in the periphery, IGF1 can cross the blood brain barrier in an activity dependent manner. IGF1 in the brain impacts learning and memory by modulating neural plasticity and excitability. Brain uptake of serum IGF1 has been shown to be impaired in AD patients, leading to less bioavailable IGF1 in the brain. Despite this, the role of IGF1 in AD has remained contentious due to conflicting reports of deleterious and neuroprotective actions. Here, we argue that this discrepancy arises from the homogenous application of IGF1 (and its effectors) and that IGF1’s neuroprotective function can be unlocked by targeting specific brain cell types. In particular, it has been shown that sensory stimulation selectively enhances IGF1 autocrine signaling in vasoactive intestinal peptide (VIP+) interneurons resulting in self-inhibition of these cells. Our preliminary analyses of *In-situ* hybridization performed in brain slices of male and female mice at different ages, showed alterations in the expression of IGF1 and its receptor (IGF1R) in VIP+ neurons of AD-relevant mice. These results, together with our preliminary analysis of dual two-photon imaging recordings of PV+ and VIP+ neurons of the auditory cortex of AD-relevant

mice, could indicate an amplified autocrine signaling in VIP+ cells and provide a proximal mechanism for impaired cortical network function.

Disclosures: A. Santi: None. **R. Monga:** None. **K. Kuchibhotla:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.12/U8

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

Support: NIH Grant MH113257

Title: Distribution and segregation of neurochemically distinct populations of cholinergic and non-cholinergic neurons in rhesus macaque basal forebrain

Authors: *H. KONDO, M. ELLIOTT, A. DUQUE;
Dept. of Neuroscience, Yale Univ. Sch. of Med., New Haven, CT

Abstract: The basal forebrain (BF) plays an important role in modulating cortical activation through its widespread cholinergic and non-cholinergic projections to the entire cortical mantle. To understand the organization of BF neuron types in the rhesus macaque (*Macaca mulatta*), we systematically examined (1) the distribution of cholinergic neurons and neurochemically distinct subpopulations of non-cholinergic neurons, along with (2) the extent to which these populations are segregated. We performed single and double-immunostaining using antibodies against choline acetyltransferase (ChAT), neuropeptide Y (NPY), parvalbumin (PV), calbindin (CB), calretinin (CR), somatostatin (SOM), and non-phosphorylated neurofilament protein (SMI-32). Our results show that the numbers of ChAT, CB, and CR neurons are substantially greater than those of PV, NPY, SOM, and SMI-32 neurons. Although ChAT, CB, and CR positive neurons are distributed throughout the rostrocaudal extent of the BF, a larger number of these neurons is present in the rostral half of the BF in comparison to the caudal half. In addition, BF ChAT+ neurons are distributed both individually and as aggregates. In NPY-immunostained sections, very dense axons and boutons were observed in the BF. We found several double-labeled neurons for ChAT/CB and some double-labeled neurons for ChAT/CR and ChAT/SOM, but so far, no double-labeled neurons for ChAT/NPY, ChAT/PV, or ChAT/SMI-32. We have not observed PV/NPY or PV/SOM double-labeled neurons either. These results show that the macaque BF contains neurochemically distinct, largely non-overlapping cholinergic and non-cholinergic neuronal subpopulations.

Disclosures: H. Kondo: None. **M. Elliott:** None. **A. Duque:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.13/U9

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

Support: NIH Grant R01AG071859
NIH Grant R01AG073826

Title: Roles of Dietary Vitamin A in Dentate Gyrus Granule Cell Excitability in a Mouse Model of Alzheimer‘s Disease

Authors: *D. SELF[1,2,3], S. SALINAS[1,2], C. ZHANG[1,2], J. J. LAWRENCE[1,2,3,4];
[1]Dept. of Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Garrison Inst. on Aging, Lubbock, TX; [3]TTUHSC Grad. Sch. of Biomed. Sci., Lubbock, TX; [4]Ctr. for Membrane Protein Research, Ctr. of Excellence for Translational Neurosci. and Therapeut., Ctr. of Excellence for Integrative Hlth., Lubbock, TX

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by deficits in learning and memory. Epileptiform activity originating from the hippocampal dentate gyrus is associated with AD progression in both humans and preclinical models. Individuals with AD are more likely to be vitamin A deficient (VAD) than healthy age-matched controls. Conversely, pro-VA/VA supplementation (VAS) has been shown to possess anticonvulsive properties. Dentate gyrus granule cell (DGGC) excitability and action potential (AP) kinetics were measured using 299 whole-cell patch-clamp recordings from acute brain slices from 76 early-stage (4-month-old) J20 AD mice, with age-matched controls of both sexes. We used linear mixed-effects models (LMEM), which included the access resistance to account for the low-pass filter behavior of the access resistor. DGGCs in J20 mice from both sexes did not show altered overall excitability, but excitability was reduced by dietary VAS in a sex- and genotype-dependent manner. We observed a sex-dependent effect of genotype on AP kinetics, with female J20 DGGC APs broader than those from wild-type controls; conversely, male J20 DGGC APs were narrower (LMEM, interaction of current step with sex, and genotype; both $p<0.001$, $n=299$). In males, we hypothesize that AP narrowing is compensatory, reflecting increased current density of Na^+/K^+ ion channels. In females, AP broadening may underlie generalized network hyperactivity. VAS normalized AP kinetics in both sexes (LMEM, interaction of current step, genotype, and diet; $p<0.001$, $n=299$). Finally, we analyzed burst firing on a per-current-step basis in DGGCs using a novel machine learning approach. Burst firing was reduced in J20 animals and increased with VAS, and we observed sex differences (generalized linear model, main effects of sex and diet, $p<0.05$, $n=299$; interaction of current step with diet, sex, and genotype, all $p<0.001$, $n=299$). Burst firing, which is reliant on calcium homeostasis, may be important for pattern separation and memory encoding. Burst firing was increased by VAS in both sexes, implying that VAD contributes to AD progression. Therefore, dietary VAS may avoid pathological changes in DGGC excitability associated with pattern separation deficits in the early stages of AD. Experiments are ongoing with mice on a VAD diet. We expect that AD-associated deficits will be larger in VAD animals and that impaired burst firing will be associated with J20 AD/VAD mice. Overall, this work supports the hypothesis that early VAS

intervention modifies DG function in a sex-dependent manner, thereby delaying excitability changes associated with AD pathogenesis.

Disclosures: D. Self: None. **S. Salinas:** None. **C. Zhang:** None. **J.J. Lawrence:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.14/U10

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

Title: Adult Hippocampal Neural Progenitor Cells (AHNPCs) Rescue Cognitive Deficits in 5XFAD Alzheimer mouse model

Authors: Y.-F. HUNG[1], S.-J. CHENG[2], ***H.-J. CHENG**[3];
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Abstract: Alzheimer’s disease (AD) is characterized by cognitive decline and memory impairments. The loss of neuronal and synaptic function begins in the early stage of AD, before amyloid plaques and neurofibrillary tangles have formed. In this study, we generated adult hippocampal neural progenitor cells (AHNPCs) from 3m WT mice and transplanted them into the dentate gyrus (DG) of aged WT and 5XFAD mice. 5XFAD mice with AHNPCs improved cognitive abilities. While most previous studies using transplanted stem cells have shown cell aggregates in the brain, the transplanted AHNPCs migrated out, differentiated, and integrated into local neural circuits. The transplanted AHNPCs eventually became granule cells (GCs) that exhibited electrophysiological properties similar to those of endogenous GCs. Interestingly, the amyloid plaques and immune inflammatory responses in the transplanted 5XFAD mice were not affected. Together, our results suggest that restoring neuron loss by AHNPCs might provide a novel therapy approach for Alzheimer’s disease.

Disclosures: Y. Hung: None. **S. Cheng:** None. **H. Cheng:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.15/U11

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

Support: VA Merit I01-BX004646
NIA Grant R01-AG076030
NINDS Grant T32-5NS082145
VA Merit I01-BX004693

Title: Perimenopausal Endocrine Dysfunction Exacerbates Hippocampal Circuit Pathology and Cognitive Decline in a Preclinical Model of Alzheimer's Disease

Authors: *K. LILLY, S. M. PEREZ, D. J. LODGE;
UT Hlth. San Antonio, San Antonio, TX

Abstract: Alzheimer's disease (AD) affects nearly 7.5 million individuals over the age of 65, with women representing almost two-thirds of diagnosed cases. While this sex difference has historically been attributed to longevity, emerging evidence suggests that endocrine changes during the menopausal transition may directly contribute to AD vulnerability. Indeed, women transitioning through menopause exhibit increased amyloid beta (Aβ) deposition and accelerated gray and white matter loss, suggesting that ovarian aging may interact with AD-related pathology. The hippocampus, a primary site of AD pathology, exhibits network hyperexcitability driven in part by disruptions in excitatory/inhibitory balance. Similar hippocampal hyperactivity is observed during the perimenopausal transition, suggesting that endocrine aging and AD may converge on common circuit mechanisms. We hypothesize that perimenopause represents a critical window during which endocrine disruption exacerbates hippocampal dysfunction and accelerates AD-related cognitive decline. To test this, we combined the 4-vinylcyclohexene diepoxide (VCD) model of ovarian transition with transgenic Alzheimer's disease rats expressing human amyloid precursor protein and presenilin-1 mutations. Animals underwent longitudinal hippocampal-dependent behavioral testing from 4.5-12.5 months of age, paired with monthly in vivo electrophysiological recordings of dorsal hippocampal activity in awake, freely moving animals. Preliminary results demonstrate that VCD treatment potentiates spatial memory deficits in TgAD rats, while recognition memory impairments appear primarily genotype independent. Electrophysiological recordings reveal early elevations in interneuron activity in both TgAD and VCD-treated animals that follow an inverted U-shaped trajectory consistent with age-related alterations in hippocampal network function. Importantly, these changes appear dependent on the AD genotype. Finally, complementary cell culture studies will examine the relative contributions of rising follicle-stimulating hormone (FSH) and estrogen depletion to neuroinflammatory signaling. Together, these studies identify the menopausal transition as a critical period of hippocampal vulnerability and examine FSH as a potential mechanistic contributor to female-specific AD risk.

Disclosures: K. Lilly: None. **S.M. Perez:** None. **D.J. Lodge:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.16/U12

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

Support: NIH R01DC021595
NIH R01NS116598
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Hearing Research Inc.
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Coleman Memorial Fund
UCSF RAP Fund

Title: Auditory hyporesponsivity in hippocampus as a biomarker of Alzheimer's disease

Authors: *G. BLUE[1], J. BIGELOW[2], A. R. HASENSTAUB[1];
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Abstract: Alzheimer's disease (AD) features an extended preclinical phase where traditional cognitive assessments are insensitive to early pathology. Recent findings suggest sensory processing measures could serve as non-invasive biomarkers for early detection. Although hippocampus (HC) is classically characterized as a center for spatial processing and memory formation, we recently demonstrated that many HC neurons in naïve mice respond to passive environmental sounds, particularly broadband noise onsets. Because AD pathology emerges in HC before spreading to the cortex and elsewhere, we hypothesize that sound-evoked responses in HC could provide a novel, early signal of circuit dysfunction in AD. To investigate this, we conducted extracellular recordings with Neuropixels probes spanning auditory cortex (ACtx), HC, and the medial geniculate body (MGB) in awake, head-fixed 5XFAD mice and wildtype littermates. Mice were tested at a mild symptomatic stage (6-8 months), a timepoint at which amyloid-β plaque accumulation is advanced in HC and also present in ACtx and MGB. We found that HC neurons in 5XFAD mice exhibit a striking hyporesponsivity to sound. Relative to WT controls, substantially fewer HC neurons in 5XFAD mice responded to repeating broadband noise trains (~4 Hz) across all tested sound levels (35-85 dB). Moreover, HC neurons in 5XFAD mice typically responded only to the initial onset of the noise train, failing to track subsequent repeats. This hyporesponsivity evident in single-unit responses was mirrored in neural population measures including multiunit spiking and local field potentials. In addition, sound-evoked face movements, which correlate with population-level responses in HC, were also significantly attenuated in 5XFAD mice compared to WT littermates. Critically, auditory brainstem responses did not differ between genotypes, implicating central rather than peripheral dysfunction. Our findings thus suggest passive responses to sounds could serve as readout of HC network dysfunction in AD.

Disclosures: G. Blue: None. **J. Bigelow:** None. **A.R. Hasenstaub:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.17/U13

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

Title: Live concert music modulates stress, social connection, and inter-brain synchrony compared to pre-recorded concert music

Authors: *D. A. WATTS[1], C. S. AKAFIA[1], S. DAYAL[1], D. RAYFORD[1], S. SAEDI[1], P. TOOTLE[1], J. A. DELINOIS[1], A. TURK[1], M. NANDIGAM[1], S. LEE[1], N. JAIN[1], G. A. ALAYINE[2], A. ALLSOP[1];
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Abstract: Music interventions are increasingly used in dementia care; however, the mechanisms of the effects of these interventions have not been thoroughly elucidated, and the value of live performance compared with recorded music requires further investigation. This study examines the effects of live music on neural activity, synchrony, and self-reported well-being in people with early-stage Alzheimer's disease (AD) or dementia, their caregivers, and older and younger controls. We hypothesized that, compared to recorded music, live music would reduce anxiety, increase motivation for social connection, and enhance synchrony between AD-caregiver dyads. Participants (n = 48) were categorized into four groups: Alzheimer's / Dementia (AD; n = 5; mean = 71.4 years), Caregiver (CG; n = 4; mean = 75.5 years), Age-matched control (AMC; age ≥ 50; n = 15; mean = 67 years), and Younger control (YC; age < 50; n = 24; mean = 27.1 years). Individuals attended a live performance and a viewing of a pre-recorded playback of a concert over two sessions, one week apart. Electroencephalogram (EEG) and psychometric data were collected during each session. Self-reported scales included the State-Trait Anxiety Inventory (STAI), Patient Health Questionnaire-9 (PHQ-9), Quality of Life Scale (QOLS), and State Motivation to Foster Social Connections Scale (SMFSCS).
Across the full cohort, live music was associated with a significant reduction in STAI, while both live and recorded music produced significant reductions in PHQ-9 scores. The YC group demonstrated the broadest psychometric response, with significant improvements in depression, anxiety, and social motivation. Individuals in the AMC group showed PHQ-9 scores after music listening, and QOLS scores improved among age-matched controls and caregivers after live music. AD and caregiver groups trended toward improvement across multiple measures without reaching significance.
In EEG, the AD group showed significant differences in power spectral density relative to age-matched and younger controls. However, given the small AD sample, the most robust spectral differences were observed between AMC and YC groups. EEG synchrony analysis showed differences in inter-subject synchrony in AD-caregiver dyads between live music and playback. This study finds that live music was associated with reduced anxiety and improved quality of life with qualitative reports of emotional regulation and social connection. Together with multimodal bio-signal measures collected, these preliminary finds support further investigation of how live and recorded music differentially affect brain and body in dementia care.

Disclosures: D.A. Watts: None. **C.S. Akafia:** None. **S. Dayal:** None. **D. Rayford:** None. **S. Saedi:** None. **P. Tootle:** None. **J.A. Delinois:** None. **A. Turk:** None. **M. Nandigam:** None. **S. Lee:** None. **N. Jain:** None. **G.A. Alayine:** None. **A. Allsop:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.18/U14

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

Support: NIH Grant R01AG092683
NIH Grant R61AG094667

Title: Route Learning Impairments and PV Interneuron Dysregulation in the Posterior Parietal Cortex of Alzheimer's Mouse Models

Authors: *N. VISHWAKARMA[1], Z. CHENG[2,3], N. OHASHI[6], K. PARK[4], J. SHIN[5], P. HONMA[7], J. J. PALOP[8];
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Abstract: To navigate, the brain must transform spatial representations of the external environment into body-centered, goal-directed routes. This transformation depends critically on the posterior parietal cortex (PPC). Recordings from freely moving rodents have shown that PPC excitatory neurons encode heading direction, velocity, and progress along a route. However, the contributions of inhibitory interneuron subtypes to this encoding remain largely unexplored. Parvalbumin-expressing (PV) interneurons coordinate network synchrony and regulate the timing of spatially-tuned neurons, and their silencing in the PPC disrupts sensory-guided behavior. Therefore, we hypothesize that PV interneurons contribute to the encoding of self-motion and route structure and that their dysfunction impairs the transformation of spatial representations into goal-directed navigation. This is particularly relevant in Alzheimer's disease (AD), where early impairments in spatial planning and navigational flexibility may reflect disruptions in PPC-mediated integration of internal goals with spatial information. To investigate these processes, we developed a novel behavioral paradigm to assess route planning and navigational flexibility using a "harpin maze". Mice traverse repeating segments connected by tight, hairpin turns to reach a reward, and two distinct reward locations were evaluated. A complete "task-relevant bout" is defined as continuous traversals from the start zone to the reward zone then back to the start zone, whereas incomplete, "non-task-relevant bouts" prematurely reverse direction before reaching the start zone. Using this paradigm, we found that multiple AD mouse models, including App-KI, APOE4, and APP-tg mice, performed more bouts of all types, including both task-relevant bouts and non-task-relevant bouts, suggesting increased locomotor activity that reflects inefficient, rather than improved, goal-directed navigation. However, whether disrupted PV interneuron activity contributes to these navigational deficits in AD has not been examined. Thus, we will present both the electrophysiological activity of PPC PV interneurons and the behavioral performance in wildtype, knock-in, and transgenic AD mice

during hairpin maze navigation to determine how PV interneuron dysfunction contributes to route planning and navigational flexibility in AD.

Disclosures: N. Vishwakarma: None. **Z. Cheng:** None. **N. Ohashi:** None. **K. Park:** None. **J. Shin:** None. **P. Honma:** None. **J.J. Palop:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.19/U15

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

Support: R01AG092683
R61AG094667

Title: VAME-Based Behavioral Segmentation Reveals Functional Clustering of GABAergic Interneurons in Health and Their Disruption in Alzheimer's Disease Mouse Models

Authors: *K. PARK[1,2], S. MILLER[1,2], Y. ZHANG[1,2], S. BANGERA[1,2], J. SHIN[1,2], J. J. PALOP[1,2];
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Abstract: Alzheimer’s disease (AD) is characterized by cognitive deficits and widespread neural network dysfunction, including impaired GABAergic interneuron function. Recent studies have revealed that spontaneous behavioral abnormalities emerge before cognitive deficits can be detected, but the underlying circuit mechanism of these preclinical alterations is poorly understood. Here, we investigated how GABAergic interneurons in the posterior parietal cortex (PPC), one of the brain regions for goal-oriented planning, contribute to spontaneous behavioral deficits in AD. We combined in vivo Ca^{2+} imaging using AAVs targeting selectively GABAergic interneuron cell type with a head-mounted miniscope in freely behaving wildtype (WT) and AD mouse models (5xFAD). Concurrent behavior was recorded and pose was estimated via DeepLabCut. Behaviors were segmented into 20 unsupervised motifs using a machine learning tool, ML-MAVE for latent behavior embedding. First, we investigated how PPC interneurons are related with speed. In WT mice, majority of PPC interneurons showed preferred firing to high speed, resulting in positive correlation at population level. In contrast, interneurons in 5xFAD mice showed decreased sensitivity to speed and preference to low speed, leading weakened speed tuning. To further investigate if PPC interneurons are related with spontaneous behaviors, we clustered PPC interneurons based on their activities during 20 ML-VAME motifs. We could organize PPC interneurons into three functional clusters, which were selectively responsive to horizontal movement (cluster 1), vertical movement (cluster 2), or minimally to behavior (cluster 3). In WT mice, majority of PPC interneurons were either cluster 1 or 2, while most of them were cluster 3 in 5xFAD mice. Moreover, cluster 1 or 2 neurons in 5xFAD mice showed reduced selectivity to horizontal and vertical movement, respectively, suggesting disrupted functional

clusters of PPC interneurons in 5xFAD mice. Our results suggest that functional disorganization of GABAergic circuits in PPC may underlie spontaneous behavior deficits in early AD, offering a potential biomarker for early network pathology and a target for circuit-level interventions. Future work will dissect which GABAergic subtypes contribute to this functional clusters impairments in AD.

Disclosures: K. Park: None. **S. Miller:** None. **Y. Zhang:** None. **S. Bangera:** None. **J. Shin:** None. **J.J. Palop:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.20/U16

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

Support: NIH R01MH108342
NIH R01AG066489

Title: Reduced NPY levels in prodromal TgF344-AD rats

Authors: *A. F. BARTLEY[1], J. B. LOGUE[2], G. A. GAGE[1], N. L. JACKSON[2], P. E. PONCE[1], C. M. HERNANDEZ, III[3], L. L. MCMAHON[2], L. E. DOBRUNZ[1];
[1]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]Univ. of Virginia, Charlottesville, VA; [3]Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Neuropsychiatric symptoms related to emotional processing are core features of Alzheimer's disease (AD), with anxiety occurring in ~40% of patients. Anxiety is commonly observed during prodromal AD (before memory loss); however, the cause of anxiety in prodromal AD is unknown. Neuropeptide Y (NPY), the primary anxiolytic neuropeptide in the brain, is one of the top ten hub genes in AD. NPY levels and the number of NPY-expressing cells are reduced in postmortem AD tissue, suggesting NPY loss could contribute to anxiety in AD. However, little is known about the time course of NPY changes in AD, especially in prodromal AD. To investigate this, we use the novel TgF344-AD rat model that co-expresses mutant human amyloid precursor protein (APPsw) and presenilin 1 (PS1ΔE9). TgF344-AD rats recapitulate the five major features of human AD, including age-dependent Aβ plaque accumulation. Here, we used immunohistochemistry and ELISA to measure NPY levels in hippocampus and amygdala, two brain regions important for anxiety. Our preliminary data show a decrease in NPY staining of basolateral amygdala, as well as the hippocampal stratum lacunosum-moleculare layer, of TgF344-AD rats compared to wild-type rats at 9 months of age, when Aβ plaque accumulation is elevated. Interestingly, in both regions, GABAergic NPY-expressing interneurons have dystrophic morphological features at this age. Previous studies have shown that other GABAergic interneuron subtypes are dystrophic starting at 12 months of age; our data therefore suggest that NPY-expressing cells could be more sensitive in AD.

Overall, our preliminary data suggest that dysfunction of the NPYergic system in prodromal AD could contribute to circuit dysfunction in brain regions that regulate anxiety.

Disclosures: A.F. Bartley: None. **J.B. Logue:** None. **G.A. Gage:** None. **N.L. Jackson:** None. **P.E. Ponce:** None. **C.M. Hernandez:** None. **L.L. McMahon:** None. **L.E. Dobrunz:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

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Program #/Poster #: PSTR260.21/U17

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

Support: NIH Grant 5R01AG066489

Title: Regional Alterations in Neuropeptide Y Interneurons in Models of Alzheimer's Disease and Down Syndrome

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Abstract: Down syndrome (DS) confers a markedly increased risk for early-onset Alzheimer's disease (AD), making it a genetically defined model of accelerated AD-related neurodegeneration. While AD is associated with early network hyperexcitability, DS exhibits excessive inhibitory tone. Despite these contrasting network states, both are linked to cognitive decline and circuit dysfunction, suggesting shared mechanisms of network instability. Notably, although DS is characterized by excessive inhibitory tone, both DS and AD exhibit circuit dysfunction and cognitive decline, suggesting that disrupted interneuron coordination or network integration, rather than absolute levels of inhibition, may represent a shared mechanism of network vulnerability. However, the circuit changes that may connect early inhibitory abnormalities in DS to later AD-related pathology remain poorly understood.Neuropeptide-Y (NPY)-expressing interneurons are key regulators of hippocampal (HPC) excitability, synaptic stability, and network synchronization underlying cognition and memory. However, their role in linking developmental alterations in inhibitory circuitry to AD-related hyperexcitability and progressive network dysfunction across DS and sporadic AD remains unclear.In this study, NPY interneuron populations were quantified by immunofluorescence in the CA1 and dentate gyrus (DG) regions of HPC in 9-month-old Dp16 mice and 18-month-old TgF-344 rats relative to WT littermates (n=3 males per genotype). Results showed elevated NPY expression in both CA1 and DG of Dp16 mice relative to WT controls. In AD, TgF-344 rats showed a marked reduction in NPY expression in CA1 and DG relative to WT controls. NPY has also been implicated in

maintaining blood-brain barrier (BBB) integrity, and both DS and AD models exhibit increased BBB permeability, suggesting that neurovascular dysfunction may interact with inhibitory circuit alterations to influence network stability.Together, these findings implicate NPY-associated inhibitory circuitry and neurovascular pathways as potential contributors to a shared circuit vulnerability linking early network alterations in DS to increased susceptibility to AD-related pathology.

Disclosures: A. Adkins: None. **B. Duncan:** None. **A. Brandebura:** None. **L.E. Dobrunz:** None. **L.L. McMahon:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

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Program #/Poster #: PSTR260.22/U18

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

Support: NIH Grant 5R01AG066489

Title: Blood-Brain Barrier Dysfunction in Alzheimer’s Disease and Down’s Syndrome

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[1]Neurosci., Univ. of Virginia, Charlotteville, VA; [2]Neurosci., [3]Dept. of Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by cognitivedecline, neuroinflammation, and blood-brain barrier (BBB) dysfunction. It is also understood thatnearly all individuals with Down’s Syndrome (DS) develop early-onset AD during their lifetime.Interestingly, individuals with DS display similar BBB dysfunction seen in sporadic AD prior to thedevelopment of AD pathology. This raises the question whether BBB breakdown is an early driver ofAD pathology, a downstream consequence of Aβ/pTau accumulation, or part of a reciprocalfeedback loop that accelerates neurodegeneration. In this study, we begin to explore the timecourse of the breach in the BBB the CA1 and dentate gyrus (DG), regions in the hippocampusimpacted by neurodegeneration during progressive AD and associated with memory and spatialbehavior deficits.Using immunofluorescence imaging, we quantified total number of astrocytes and astrocytemorphology using GFAP, and fibrinogen extravasation as a marker of BBB breach in CA1 and DG in9-month old male Dp16 mice (n=3) and wild-type (WT) littermates (n=3), and 18-month old maleTgF344-AD rats (n=3) and WT littermates (n=3).Significant changes in astrocyte morphology were observed. In TgF344 rats, we observed higherstaining intensity for GFAP, and a smaller number and length of processes coupled with lowernumber of branchlets, suggesting reactive morphology compared to WT littermates who exhibitedfibrous and radial astrocyte morphology, possessing a greater number of processes with moreassociated branchlets. In Dp16 mice, astrocytes exhibit a reactive phenotype compared with wild-type controls, characterized by hypertrophic morphology,

increased hippocampal GFAP-positivestaining area, and altered spatial clustering. In both Tg344 rats and Dp16 mice, fibrinogenextravasation was increased relative to WT littermates.These findings suggest increased permeability of the BBB can be investigated using fibrinogenstaining in both TgF344 and Dp16. This similar phenotype perhaps leads to the reactive morphologyof astrocytes in the TgF344 and Dp16 models. However, the diYerences in overall morphology andorganization of astrocytes suggest upstream genetic factors conferring diYerential response to BBB permeability in DS and AD.

Disclosures: B. Duncan: A. Employment/Salary (full or part-time):; Research Technician, University of Virginia. **A. Adkins:** None. **L.L. McMahon:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

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

Support: 3R01AA027706 - 04W1
NIA R01 AG066489

Title: Effects of adolescent intermittent ethanol exposure on hippocampal CA1 pyramidal cell excitability in wild type rats and in the TgF344-AD rat model of Alzheimer’s disease

Authors: *J. B. LOGUE[1], L. L. MCMAHON[2];
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Abstract: Human studies suggest that ethanol consumption may present increased risk for developing Alzheimer’s disease (AD). Studies in TgF344-AD rats show ethanol exacerbates AD pathology, with adolescent ethanol exposure leading to worse performance in memory tests. In this study, we investigated whether ethanol exposure accelerates dorsal hippocampal CA1 pyramidal cell dysfunction in male TgF344-AD rats compared to wildtype (WT). Rats were exposed to either air or adolescent intermittent ethanol (AIE) in inhalation chambers from postnatal day 28 to 56. An additional TgF344-AD cohort was exposed to a second ethanol exposure, chronic intermittent ethanol (CIE), between postnatal days 70-91. We used whole-cell patch clamp slice electrophysiology to record CA1 pyramidal cells in 4-month-old rats (7 groups, N=5 per group, n=9-11 cells per group), an age prior to accumulation of amyloid beta plaques in the TgF344-AD model, to determine the impact of ethanol exposure on neuronal function. We found no detectable effect of genotype or ethanol exposure on resting membrane potential or spontaneous firing. We observed a genotype specific effect of treatment, with ethanol increasing evoked action potential firing in CA1 pyramidal cells in WT rats ($p=0.033$). However, ethanol decreased evoked action potential firing in CA1 pyramidal cells in TgF344-AD rats ($p=0.039$). The decreased excitability of CA1 pyramidal cells in TgF344-AD following ethanol exposure

requires intact synaptic transmission, and a second exposure to ethanol had no additional effect. Together, these data show increased baseline excitability of CA1 pyramidal cells in TgF344-AD rats, with ethanol reducing synaptically driven excitability in the TgF344-AD model.

Disclosures: J.B. Logue: None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

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

Support: R01AG071745
F30AG082448
R35CA283926

Title: APOE4 and doxorubicin impair inhibitory interneuron function and homeostatic regulation in the entorhinal cortex

Authors: *N. LUO[1], H. PANDIT[3], S. KALRA[2], J. MANDELBLATT[3], S. VICINI[4], G. W. REBECK[5];
[1]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [2]Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Bryn Mawr, PA; [4]Dept Parmacology & Physiol., [3]Georgetown Univ. Med. Ctr., Washington, DC; [5]Neurosci., Georgetown Univ., Washington, DC

Abstract: APOE4 is a risk factor for several disease states associated with cognitive impairment, including Alzheimer’s disease and cancer-chemotherapy induced cognitive impairment. Using mouse knock-in models of human APOE alleles, we examined the effects of APOE genotype and chemotherapy on the ex vivo electrophysiological characteristics of excitatory and inhibitory neurons in the entorhinal cortex (EC). We found that APOE4 is associated with a significantly higher excitatory/inhibitory ratio (0.33 ± 0.04) in the layer 2/3 pyramidal cells of the entorhinal cortex compared to APOE3 (0.19 ± 0.04). We crossed APOE mice to mice with parvalbumin (PV) interneurons tagged with tdTomato, allowing us to measure effects specifically on this inhibitory cell type. For EC pyramidal neurons, the chemotherapeutic agent doxorubicin caused increases in the amplitudes of both spontaneous excitatory and inhibitory post-synaptic currents, with significant responses ($^{***}p < 0.001$; $^{**}p < 0.01$ respectively) in APOE3 brains. For EC PV neurons, APOE4 genotype was associated with significantly lower firing rates at injections of high currents ($^{**}p < 0.01$), but rates were unaffected by doxorubicin. Doxorubicin doubled the percentage of PV cells that showed inactivation block in APOE3 brains (25% to 52%) but had no effect on APOE4 brains (50% to 54%). This ex vivo study suggests that APOE4 impairs homeostatic synaptic transmission in pyramidal cells under control conditions and causes a lack of responsiveness to a stressor (doxorubicin treatment) in PV cells.

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Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.25/U21

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

Support: NIH R21 AG089715-02

Title: Cell Type-Specific Contributions to Early Stage Hyperexcitability in Alzheimer’s Disease

Authors: *A. ASH[1], J. DOLAN[2], C. VARGAS[3], C. KANZLEMAR[4], **S. HUSSAINI**[5]; [1]Nathan Kline Institute/NYU, Orangeburg, NY; [2]Nathan Kline Institute/NYU, SLEEPY HOLLOW, NY; [3]Nathan Kline Institute/NYU, Port Chester, NY; [4]Nathan Kline Institute/NYU, Ossining, NY; [5]Th Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Early circuit dysfunction in the medial entorhinal cortex (MEC) is a hallmark of Alzheimer’s disease (AD) and may underlie spatial deficits and memory impairments observed at disease onset. The specific neuronal populations driving its vulnerability to amyloid-β (Aβ) and tau pathology remain poorly defined. This study interrogates cell type-specific contributions to determine whether AD-associated hyperexcitability arises from increased firing of excitatory neurons, reduced activity of inhibitory interneurons, or a combination of both. As well, we will assess how the excitatory/inhibitory balance shifts over time, looking at younger and older animals as disease progresses. Using optogenetic and chemogenetic approaches combined with in-vivo electrophysiology in AD transgenic mice, APP(NL-G-F)/MAPT(S305N/10+3G), and wild-type control mice, we will characterize excitatory and inhibitory neuronal activity within the MEC and assess whether selective excitement or suppression modulates network stability. Using optogenetic tagging, we will dissect contributions of excitatory neurons, parvalbumin-positive (PV^+) and somatostatin-positive (SST^+) interneurons to MEC dysfunction (via ChRmine expression under CaMKIIα promoter or with Cre-On ChRmine-DIO AAV with PV- and SST-Cre lines). Then chemogenetic modulation (hM3Dq or hM4Di DREADDs) in these populations will test whether normalizing excitatory activity restores network function and reduces pathology. Preliminary results show AD transgenic animals have hyperexcitability in the MEC neuron population, with significantly increased firing rates compared to wild-type controls. Additionally, AD mice have reduced spatial information coding ability in MEC neuronal activity compared to WTs. Identifying the excitatory and inhibitory mechanisms underlying hyperexcitability will provide mechanistic insight into early AD circuit failure, define cell-type-specific therapeutic targets, and inform the design of sensitive functional biomarkers for early diagnosis and intervention.

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Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

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Program #/Poster #: PSTR260.26/U22

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

Support: NIH, R01AG081981

Title: Ex vivo neuronal network activity and single-neuron recordings show disrupted hippocampal CA1 outputs in 5xFAD mice

Authors: *W.-C. CHANG[1], G. G. MURPHY[2];
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Abstract: Hallmark features of Alzheimer's disease (AD) include amyloid beta (Aβ) deposition and cognitive decline. While the toxicity of Aβ is undeniable, mounting evidence suggests that neurons are susceptible to Aβ through multiple pathways. Early and aggressive Aβ production in a 5xFAD mouse model of AD, in which nicotinamide nucleotide transhydrogenase (NNT) is deleted, suggests that mitochondrial dysfunction and oxidative stress are critical to the progression of AD. Using ex vivo neuronal network activity as a structural and functional biomarker, along with single-neuron recordings, we assessed the vulnerability of the hippocampus in normal aging mice and AD models with or without NNT. Horizontal slices (400 μm) containing the hippocampus and the entorhinal cortex (EC) were prepared from 12±1 months old mice, and artificial cerebrospinal fluid containing no Mg^{2+} and high K^{+} (8 mM) was used to induce spontaneous neuronal network activity. Network activity occurred regularly (inter-event intervals, IEI = 2.9±0.8 seconds) in the slices from the normal aging mice, but network activity formed quasi-periodic clusters (28.1±5.7 seconds long, IEI = 1.6±0.9 seconds) in the slices prepared from 5xFAD mice. In the normal slices recovered from aged mice, the hippocampus and the EC equally led network activity; however, in the 5xFAD slices, network activity originating from the hippocampus often failed to spread to the EC, implying CA1 output is disturbed. Single-neuron recordings showed that the CA1 pyramidal neurons in slices prepared from 5xFAD mice reached depolarization block more easily than the neurons in the normal aging group. Our preliminary data suggest that loss of NNT has no effect at this late age, but does not rule out a role at younger ages.

Disclosures: W. Chang: None. **G.G. Murphy:** None.

Poster

PSTR260: Alzheimer's Disease: Neural Circuit Disruption II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR260.27/U23

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

Support: Cure Alzheimer's Fund
RF1AG098887

Title: APOE4 Synergizes with Amyloid to Impair Sleep and Circadian Regulation

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Abstract: Apolipoprotein E ε4 (APOE4) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). Sleep and circadian disturbances are common in AD and may contribute to amyloidosis, particularly in APOE4 carriers. However, the impact of APOE4 on amyloidosis-related sleep/circadian impairments remains unclear. We hypothesized that APOE4 synergized with amyloidosis to accelerate sleep/circadian disturbances and cortical circuit dysfunction. APPswe/PS1dE9 (APP) mice were crossed with human APOE knock-in or APOE knockout (KO) mice to generate APOE4/APP, APOE3/APP, APOE-KO/APP, APOE4, APOE3 and APOE-KO cohorts. Sleep was monitored in freely moving mice using fully implantable wireless EEG/EMG telemetry. Sleep architecture was quantified using fully automated scoring pipeline to decrease experimenter bias. Locomotor activity was analyzed using fractal scaling analysis to assess multiscale activity regulation across timescales ranging from ~10 min to ~8 h, and cosinor analysis to evaluate 24-h circadian rhythmicity. Sleep-dependent brain rhythms, particularly slow oscillation (SO), were assessed using in vivo widefield voltage sensitive dye imaging under anesthetized conditions. We examined the effect of APOE-mimetic peptide CN-105 on sleep and sleep-dependent brain rhythms in APOE4/APP mice. APOE4/APP mice showed marked sleep impairments at 2 months, including reduced NREM sleep duration, increased wakefulness, and greater sleep fragmentation. In contrast, APOE3/APP mice and other control genotypes showed preserved sleep architecture at the same age. Fractal analyses revealed impaired fractal regulation of locomotor activity in APOE4/APP mice, leading to random activity fluctuations across ~10-min to ~8-h timescales. Cosinor analysis showed reduced 24-h amplitude in APOE4/APP mice, indicating dampened circadian rhythmicity. These findings suggest that APOE4 on APP background impairs sleep architecture and behavioral regulation. Widefield voltage imaging revealed reduced cortical SO power and impaired intra- and inter-hemispheric functional connectivity in 2-month-old APOE4/APP mice. These deficits emerged earlier in APOE4/APP mice compared to those in APOE3/APP mice or APP mice. Acute 1.5-day treatment with CN-105 rescued NREM sleep duration and cortical SO power in APOE4/APP mice. These results suggest that APOE4 synergizes with amyloidosis to drive early sleep and circuit dysfunction that remains amenable to therapeutic modulation. Targeting APOE-

dependent mechanisms may offer a novel therapeutic strategy to restore sleep-network integrity and reduce AD-related vulnerability in APOE4 carriers.

Disclosures: T.H. Doan: None. **Z. Liu:** None. **M. Abedin:** None. **G. Albasini:** None. **P. Li:** None. **K. Hu:** None. **C.A. Lemere:** None. **D.T. Laskowitz:** None. **K. Kastanenka:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.01/U24

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

Support: NIH Grant R01AG085545

Title: Early sulfatide loss may contribute to tau pathology in Alzheimer's disease

Authors: *S. SONG[1,2], X. LI[1], S. HE[1], X. HAN[2];
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Abstract: Alzheimer’s disease (AD) is characterized by amyloid accumulation, tau pathology, and progressive neurodegeneration. However, increasing evidence suggests that myelin abnormalities occur early in disease progression. Sulfatide, a major lipid component of myelin, is reduced in the early stages of AD and aging, but whether sulfatide loss contributes to tau pathology remains unclear.Our previous findings showed increased phosphorylated tau (p-Tau) in sulfatide-deficient models, with prominent p-Tau expression detected in oligodendrocytes. This raises the possibility that early lipid changes may influence tau pathology through mechanisms beyond neurons alone.To further investigate this relationship, we analyzed brain tissues from 3-month-old CST-deficient PS19 mice using immunohistochemistry and western blotting. Preliminary results showed increased tau phosphorylation across multiple p-Tau markers under sulfatide-deficient conditions, including AT8, PHF13, and other phospho-tau epitopes. Changes were also observed in proteins associated with cellular stress responses, energy regulation, and tau-related signaling pathways.

Disclosures: S. Song: None. **X. Li:** None. **S. He:** None. **X. Han:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.02/U25

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

Support: NIH Grant AG054018
NIH Grant AG072458

Title: The HSP90 co-chaperone ChordC1 is enriched in the Alzheimer's disease-resistant cerebellum and suppresses tau aggregation in vitro

Authors: M. SANCHEZ[1], S. PAL[2], A. ALLEN[2], *J. KURET[2];
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Abstract: Tauopathies, including Alzheimer's disease (AD), are accompanied by the progressive accumulation and prion-like trans-synaptic spread of misfolded tau, a process linked to neurodegeneration and cognitive decline. In AD, tau pathology advances through vulnerable cortical and limbic networks, yet the cerebellum remains resistant, suggesting it harbors endogenous mechanisms that buffer tau aggregation. In contrast, other tauopathies such as progressive supranuclear palsy (PSP) show severe cerebellar involvement, including tau pathology and degeneration. This differential cerebellar vulnerability provides a unique opportunity to identify proteostatic mechanisms underlying neuronal resistance to tauopathy polymorphs within the same brain region. To identify mechanisms associated with resistance to AD, we compared adaptive gene expression patterns in cerebellum with vulnerable neocortical regions across two independent human transcriptomic datasets. Differential expression, gene ontology enrichment, WGCNA co-expression, and ARACNe network inference were integrated to prioritize candidate key drivers. This analysis identified ChordC1, an HSP90 co-chaperone, as a key driver of resistance in AD cerebellum. To characterize ChordC1 interaction with tau protein, recombinant human ChordC1 was expressed in E. coli, purified to homogeneity, and tested in a cofactor-driven tau aggregation assay. Results showed that in the absence of ChordC1, tau exhibited robust aggregation, whereas ChordC1 suppressed aggregation in a dose-dependent manner, with near-complete inhibition at equimolar concentrations. In contrast, ovalbumin, a non-chaperone protein control, had little effect on tau aggregation, supporting specificity of ChordC1-mediated chaperone activity. Transmission electron microscopy confirmed the absence of detectable fibrils in ChordC1-containing reactions, indicating that ChordC1 suppresses formation of filamentous tau. To evaluate disease specificity, we measured ChordC1 protein levels in human cerebellum from cognitively normal controls, AD, and PSP cases. Immunoblot analysis revealed increased ChordC1 levels in AD cerebellum relative to controls, whereas PSP cerebellum showed no significant ChordC1 induction. Together, these findings support a model in which ChordC1 contributes to an adaptive cerebellar proteostasis network that constrains tau aggregation in AD, but is not induced in PSP, highlighting tauopathy-specific selectivity in proteostatic resistance and revealing endogenous pathways that may be leveraged to limit tau-driven neurodegeneration.

Disclosures: M. Sanchez: None. **S. Pal:** None. **A. Allen:** None. **J. Kuret:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.03/U26

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

Title: Understanding the progression of Alzheimer’s disease with site-specific phospho-tau antibodies

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Abstract: Alzheimer’s disease (AD) is a devastating cognitive neurodegenerative disorder and the leading cause of dementia in older adults. A pathological hallmark of AD are neurofibrillary tangles characterized by hyperphosphorylation and aggregation of the microtubule associated protein tau. There are over 85 potential phosphorylation sites that span the tau protein, several of which have emerged as biomarkers or are associated with distinct stages of disease onset and progression. Therefore, the accurate detection of site-specific tau phosphorylation is critical for understanding disease mechanisms, tau pathology, and targeted therapeutics for AD. However, due to epitope similarity, the generation of antibodies against specific tau phosphorylation sites is challenging and requires tactical immunogen design and thorough validation. Here, we present a panel of over 15 phospho-tau antibodies targeting key epitopes associated with distinct stages of AD pathology, including the historically difficult target site pThr217. These antibodies were evaluated in multiple immunoassay applications including western blot, ELISA, and flow cytometry, and demonstrated high specificity for phospho-tau. Furthermore, to validate site-specific recognition, we used peptide scanning, microbial display, and AI modeling to generate 3D maps of exact unique binding sites of our recombinant phospho-tau antibodies on the tau protein. Overall, our data showcases highly validated site-specific phospho-tau antibodies for the comprehensive characterization of tau in AD, from early pathological phosphorylation to advanced stages of tau pathology. These tools can be used to facilitate research on AD disease progression, biomarker discovery, and therapeutic development.

Disclosures: A. Rahman-Enyart: A. Employment/Salary (full or part-time):; Proteintech. **Y. Lu:** A. Employment/Salary (full or part-time):; Proteintech. **L. Lian:** A. Employment/Salary (full or part-time):; Proteintech. **D. Shankar:** A. Employment/Salary (full or part-time):; Proteintech.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.04/U27

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

Support: R01-AG069433 (GT, MAM)
R01AG073133 (GT)

Title: Investigating the Effects of Human Brain Derived Tau Oligomers on Cognition and Neural Stem Cell Differentiation

Authors: *A. E. TRUPP[1,2,5], K. LEU[1], G. TIMPONE[1], K. JOHNSON[1,3], B. TUMURBAATAR[4], G. TAGLIALATELA[3,4], M.-A. MICCI[1,3];
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Abstract: Adult hippocampal neurogenesis, essential for learning and memory, is profoundly disrupted in Alzheimer's disease (AD), where impaired neural stem cell (NSC) maintenance accelerates cognitive decline. AD is defined by amyloid-β plaques and neurofibrillary tangles of hyperphosphorylated tau, with oligomeric forms of each protein recognized as the most neurotoxic. A subset of individuals—non-demented with AD neuropathology (NDAN)—retain intact cognition despite harboring abundant plaques and tangles, and their resilience has been associated to preserved hippocampal NSC function and enhanced neurogenesis. The molecular mediators of this resilience remain unknown. We asked whether brain-derived tau oligomers (BDTOs) from NDAN individuals affect hippocampal neurogenesis and memory differently than those from AD patients. BDTOs were co-immunoprecipitated from postmortem AD and NDAN brain tissue and validated by western blotting and atomic force microscopy. *In vitro*, adult rat hippocampal NSCs were treated with 50nM AD- or NDAN-BDTOs or vehicle for 24 hours, allowed to differentiate for seven days, and assessed by immunofluorescence for doublecortin (DCX) and βIII-tubulin, markers for neuronal progenitors and neurons respectively. *In vivo*, adult wild-type mice received a single intracerebroventricular injection of 3µl of artificial cerebral spinal fluid (aCSF) or 3µl of 0.55µM BDTOs (AD- or NDAN-); neurogenesis in the sub-granular zone (SGZ) of the dentate gyrus (DG) was evaluated 24 hours and 10 days later by immunofluorescence using markers for NSC (SOX2/GFAP), neuronal progenitors (DCX) and neurons (NeuN). Additionally, short- and long-term memory was tested on these mice by novel object recognition (NOR). AD- and NDAN-BDTOs produced divergent effects. AD-BDTOs significantly increased NSC and neuronal progenitors both *in vitro* and *in vivo*, consistent with an accelerated differentiation phenotype that may deplete the NSC reservoir over time, whereas NDAN-BDTOs preserved a balanced differentiation timeline. Behaviorally, mice injected with AD-BDTOs showed impaired long-term memory, while those receiving NDAN-BDTOs performed comparably to aCSF-injected controls. These findings demonstrate that tau oligomers from AD and NDAN brains exert fundamentally distinct effects on NSC dynamics and on cognition. By preserving balanced NSCs dynamics and memory, NDAN-derived tau may contribute to cognitive resilience, and understanding their functional properties may reveal therapeutic targets for preserving cognition in AD.

Disclosures: A.E. Trupp: None. **K. Leu:** None. **G. Timpone:** None. **K. Johnson:** None. **B. Tumurbaatar:** None. **G. Taglialatela:** None. **M. Micci:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.05/U28

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

Support: HHMI
Freedom together foundation

Title: Molecular determinants of RNF130-mediated ubiquitination of CHIP

Authors: *X. DENG[1], J. KIM[2], J.-P. REVELLI[1], H. Y. ZOGHBI[3];
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Abstract: Carboxyl-terminus of Hsc70-Interacting Protein (CHIP) is a critical enzyme, which has a co-chaperone and an E3 ubiquitin ligase activity, targeting misfolded proteins degradation in multiple neurological disorders. We previously found that Ring finger protein 130 (RNF130) and CHIP are functionally linked through ubiquitin-mediated protein regulation: overexpression of RNF130 increases the ubiquitination of CHIP whereas its knockdown stabilizes CHIP levels. However, determining whether these effects are direct or indirect in not established. In this study, we reverted to an in vitro system to establish whether the effect is direct and map the domains mediating such regulation. Using a series of truncation and domain-mapping analyses, we determined that the Zinc-Finger and transmembrane domains of RNF130 are required for efficient binding and ubiquitination of CHIP. We further identified distinct domains within CHIP that are necessary for RNF130-mediated binding and ubiquitination. Deletion of CHIP's TPR and CC domains markedly reduced the interaction between RNF130 and CHIP, whereas loss of the U-box domain of CHIP significantly diminished the ubiquitination of CHIP by RNF130, indicating that these domains are required for efficient substrate binding and ubiquitination. Together, these results establish RNF130 as a direct E3 ubiquitin ligase for CHIP and identify the key domains in both RNF130 and CHIP that mediate substrate recognition and ubiquitination. Our findings provide mechanistic insight into the molecular basis of RNF130-dependent ubiquitination of CHIP and lay the foundation for understanding the functional consequences of this regulatory pathway in diseases.

Disclosures: X. Deng: None. **J. Kim:** None. **J. Revelli:** None. **H.Y. Zoghbi:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.06/U29

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

Support: NIH Grant F31AG081046
NIH Grant R01AG079199

Title: Characterizing the temporal progression of taupathologyin locus coeruleus of PS19 mice

Authors: *L. LU[1], A. KORUKONDA[2], D. WEINSHENKER[3];
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Abstract: Alzheimer's disease (AD) features early accumulation of hyperphosphorylated tau (p-tau) in the locus coeruleus (LC), which promotes cognitive and non-cognitive symptoms through dysregulation of noradrenergic function. The widely used PS19 transgenic mouse model expresses mutant P301S human tau throughout the brain, but the temporal progression of LC tau pathology remains under-characterized. We evaluated male and female wild-type (WT) and PS19 mice at 3, 6, and 9 months (n=3-7 per genotype/age timepoint) to establish the model as a resource for preclinical studies. Immunohistochemistry quantified tau pathology using AT8 (p-tau Ser 202/Thr 205), p-tau T231, and PHF-1 (p-tau Ser 396/Ser 404). LC structural and functional integrity were assessed via tyrosine hydroxylase (TH) and norepinephrine transporter (NET) immunoreactivity (IR). Astrocytic responses were evaluated by measuring glial fibrillary acidic protein (GFAP) IR and process density via skeletonization. Data were analyzed using a two-way ANOVA (genotype x age) and Sidak's multiple comparisons. There were significant main effects of genotype and age for pTau-T231, with PS19 mice exhibiting higher IR than WT mice and overall IR declining with age. AT8 IR demonstrated a significant genotype x age interaction, driven by marked increase in AT8 IR in 9-month PS19 mice relative to 3- and 6-month PS19. PHF-1 IR displayed a significant main effect of genotype, remaining elevated overall in PS19 mice but stable across ages. Despite this robust tau burden, LC neuronal integrity remained remarkably stable; TH IR showed no main effect of genotype or age, although a reduction of NET IR in PS19 mice was borderline significant (P=0.0645). Furthermore, GFAP analysis yielded no significant main effects or interactions, although high variance and a bimodal distribution were observed in 3-month WT and 9-month PS19 cohorts. We conclude that the PS19 model exhibits progressive LC tau pathology without immediate uniform astrogliosis or loss of LC cell bodies, but potential deterioration of the LC dendritic field.

Disclosures: L. Lu: None. **A. Korukonda:** None. **D. Weinshenker:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.07/U30

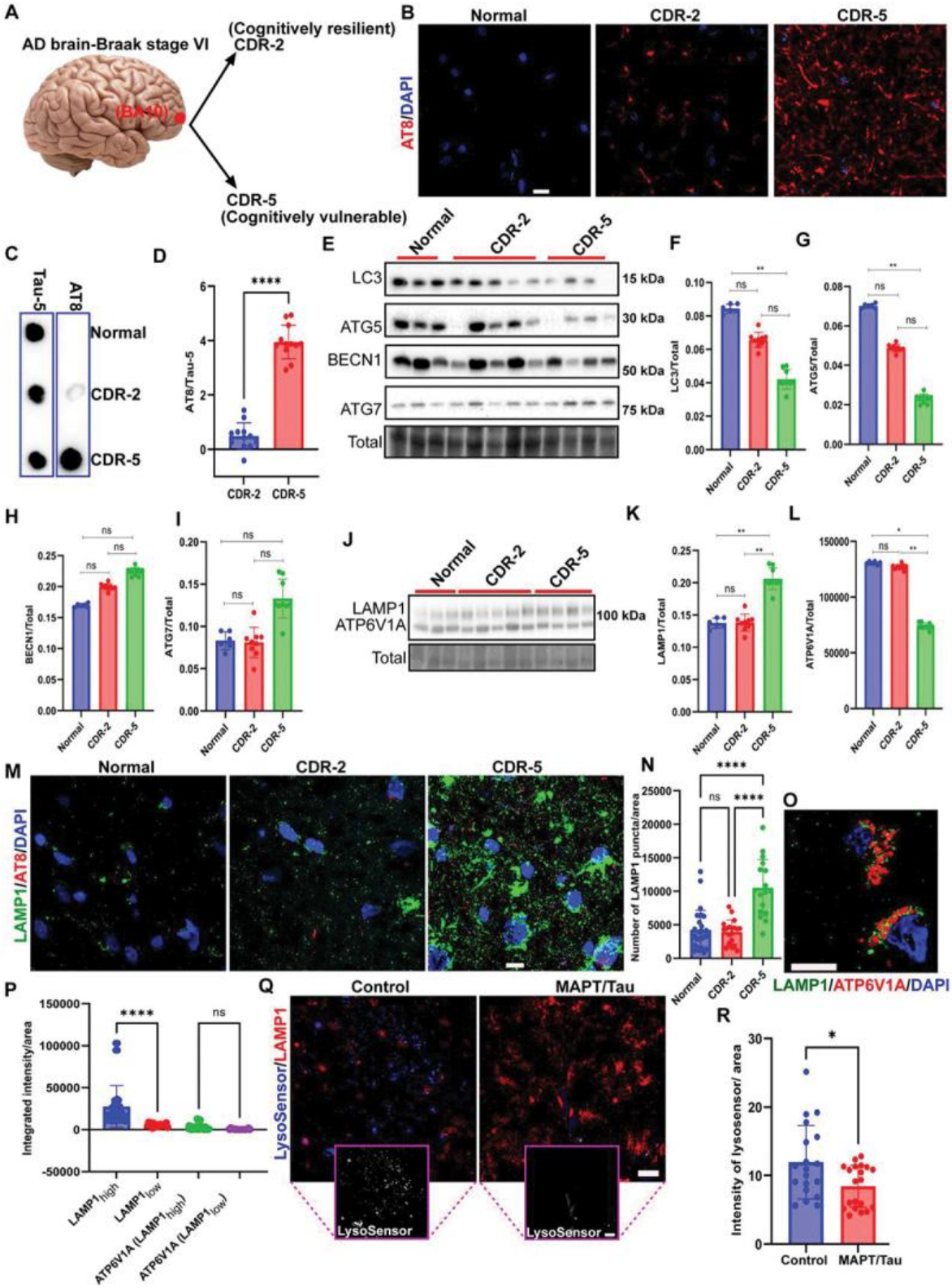
Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association-USA (23AARGD–1030306)
SERB-India (SRG2023001951)
ICMR-India (IIRPSG-2024–01–03528)

Title: Impaired Tau secretory lysosome are linked to cognitively vulnerability in Alzheimer patients.

Authors: *P. SHARMA[1,2], S. RAMAMOORTHY[3];
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Abstract: Tau pathology is strongly associated with cognitive decline in Alzheimer's disease (AD), yet individuals with comparable neuropathological burden often exhibit striking differences in dementia severity. The mechanisms underlying this cognitive resilience remain poorly understood. Here, we investigated whether lysosomal integrity influences tau pathology and cognitive outcomes in neuropathologically confirmed AD cases. Analysis of postmortem prefrontal cortex tissue from Braak stage VI individuals revealed that cognitively vulnerable patients (CDR-5) exhibited marked lysosomal dysfunction characterized by altered lysosomal acidification, increased lysosomal burden, and accumulation of tau within lysosomes, whereas cognitively resilient individuals (CDR-2) largely maintained lysosomal integrity. Biochemical, ultrastructural, and functional analyses demonstrated that lysosomes from cognitively vulnerable individuals contained partially degraded, seed-competent tau fibrils enriched in degradation-resistant amyloidogenic core regions. These lysosomal tau species retained potent seeding activity and induced synaptic loss in primary neuronal cultures. Live-cell imaging further revealed that pathogenic tau is released through lysosomal exocytosis, and inhibition of this pathway significantly reduced extracellular tau secretion. Consistent with these findings, cognitively vulnerable AD cases displayed increased lysosome-associated tau secretion and higher levels of extracellular tau assemblies. Female AD cases exhibited greater lysosomal tau accumulation and secretion than male cases. Together, these findings identify lysosomal dysfunction as a key contributor to cognitive vulnerability in AD and suggest that impaired lysosomes serve as reservoirs for pathogenic tau species that facilitate disease propagation. Preserving lysosomal integrity may promote cognitive resilience despite advanced neuropathology and represents a potential therapeutic strategy for limiting tau spread and disease progression.



Disclosures: P. Sharma: None. **S. Ramamoorthy:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.08/U31

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

Support: NIH Grant R01AG069378

Title: Examination of tangle and plaque changes in Alzheimer's disease along the gut-brain axis

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease that affects millions of people worldwide and is projected to increase to 152 million by the year 2050. The brains of AD patients are characterized by the accumulation of neurofibrillary tangles and amyloid plaques containing tau and amyloid beta (Aβ) proteins, respectively. Tau is a microtubule-associated protein that promotes microtubule stability in neurons and can be post-translationally phosphorylated. Elevated phosphorylation of tau is a typical hallmark of the neurofibrillary tangles, but it is not certain whether neurons outside of the central nervous system also accumulate this hyperphosphorylated form of the protein during disease. Similarly, it is unclear whether aggregation of Aβ into plaques occurs outside of the central nervous system during disease. The intestinal enteric nervous system is characterized by myenteric and submucosal plexi which communicate with the brain via the vagus nerve allowing bidirectional innervation. Using human male control and AD samples, western blot analysis and immunohistochemistry of the temporal cortex, vagus nerve, and colon were performed to determine whether tangle and plaque changes were observed in the vagus or colon. The well characterized anti-phosphorylated tau antibodies, AT8 and PHF-1, were used to examine epitope specific tau phosphorylation. As expected, temporal cortices demonstrated robust plaque immunoreactivity as well as tangle staining with both phospho-tau antibodies. However, there was no obvious plaque or tangle-like immunoreactivity in either the vagus or colon although some immunoreactivity was observed for both Aβ and PHF-1 in these organs. No staining was observed in the vagus or colon using the AT8 antibody. Western blot analysis revealed increased PHF-1 and AT8 immunoreactive bands in AD brains and the vagus nerve, but not in the colon. These results suggest that accumulation of neurofibrillary tangles and amyloid plaques may be unique to the central versus the enteric nervous system during AD. Moreover, tau isoform and phosphorylation sites may differ between central and enteric neurons allowing enteric neurons protection from tangle formation. Understanding the resistance of the enteric nervous system to both tangle and plaque formation may provide insight into intervention strategies for protection against disease changes in the brain.

Disclosures: J. Tallackson: None. **T. Ishida-Takaku:** None. **S. Chandrasekaran:** None. **C.K. Combs:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.09/U32

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

Title: The truncated Tau fragment 315 to 441 produced by Caspase 2 translocates to the nucleus and alters the proteome of neuroblastoma cells

Authors: *C. E. JARAMILLO[1], Y. LÓPEZ AVIÑA[2], G. MENDOZA[3], F. RODRIGUEZ CRUZ[1], A. BOUCARD, Jr.[4], F. GARCIA-SIERRA[5];
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Abstract: Alzheimer's disease (AD) symptoms arise from significant loss of neurons in the hippocampal region and the entorhinal cortex. This neuronal death is primarily caused by the abnormal aggregation of Tau protein into paired helical filaments within the somatodendritic compartment. However, the molecular mechanisms underlying this toxicity remain unclear. One contributing factor is the proteolysis of Tau, mainly mediated by Caspase 3. This abnormal post-translational modification promotes Tau aggregation and neuronal toxicity in the brains affected by AD, as well as *in vitro* cultured cells. Additionally, a new proteolytic site at Asp314, produced by Caspase 2, has been identified in AD. However, little is known about the pathological role of the Tau fragments generated by Caspase-2, specifically Tau 1 to 314 and Tau 315 to 441. In this study, we transiently transfected neuroblastoma cells with plasmids encoding either Tau 1to 314 or Tau 315 to 441 and analyzed changes in cell morphology as well as toxicity using immunofluorescence and confocal microscopy. Furthermore, we aimed to examine the physiological effects of truncated Tau expression on the overall proteome of the transfected neuroblastoma cells through mass spectrometry analysis. Our findings indicate that the Caspase 2 generated truncated Tau fragments exhibit distinct intracellular distributions, leading to the abnormal transport of Tau 315 to 441 into the nuclear compartment accompanied by the abnormal downregulation of functional and structural nuclear proteins. The generation of Caspase 2 derived truncated Tau fragments may represent an additional mechanism of neuronal toxicity occurring at early stages of the disease, prior to the filamentous aggregation of the Tau protein.

Disclosures: C.E. Jaramillo: None. **Y. López Aviña:** None. **G. Mendoza:** None. **F. Rodriguez Cruz:** None. **A. Boucard:** None. **F. Garcia-Sierra:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.10/V1

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

Support: AARF-22-926617

Title: Disease-associated tau impairs mitochondrial homeostasis and neuronal function

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Abstract: Aggregated and aberrantly modified microtubule-associated protein tau is a pathological hallmark of Alzheimer's disease (AD); however, the biological functions of tau that contribute to neuronal dysfunction remain poorly understood. Mitochondrial dysfunction is a prominent feature of AD and contributes to synaptic failure and neurodegeneration. Despite evidence linking tau pathology to mitochondrial abnormalities, the mechanisms by which disease-associated tau alters normal tau function and disrupts mitochondrial homeostasis remain unclear. In this study, we investigated how wild-type tau supports, and disease-associated tau variants impair, mitochondrial function and neuronal health. Wild-type tau and disease-associated tau variants were expressed in mammalian cells and primary mouse neurons to evaluate their interactions with mitochondria and their effects on mitochondrial integrity. Mitochondrial isolation and fluorescence microscopy demonstrated a direct association between tau and mitochondria, with wild-type tau exhibiting greater mitochondrial enrichment than disease-associated variants. Functional analyses revealed that wild-type tau maintained proper mitochondrial membrane potential, ATP production, and the level of proteins involved in mitochondrial dynamics, whereas disease-associated tau variants impaired these processes. Together, these findings identify a previously underappreciated role for tau in maintaining mitochondrial homeostasis and suggest that disease-associated tau variants compromise this function, thereby increasing neuronal vulnerability. Targeting pathological tau species or enhancing mitochondrial homeostasis may therefore represent promising therapeutic approaches for restoring neuronal function in AD and related tauopathies.

Disclosures: C.A. Garcia: None. **B. Hernandez:** None. **J. Tseng:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.11/V2

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

Support: NIH Grant R01AG085638-01A1

Title: Cortical Atrophy in Alzheimer's Disease Relates to Local Tau Deposition and Depends on Functional Segregation and Temporal Stability

Authors: *A. T. KAHN[1], D. S. JIN[1], J. PERUCHO[2], Y.-H. FANG[2], K. M. VISSCHER[1];
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Abstract: Alzheimer's disease (AD) is characterized by amyloid-β and tau accumulation, cortical atrophy, disrupted functional connectivity, altered network dynamics, and progressive cognitive decline. Tau pathology is spatially heterogeneous and may disrupt large-scale functional networks that support cognition, but it remains unclear whether tau-related deterioration acts primarily locally or whether the impact is distributed across cortex.
We used multimodal Alzheimer's Disease Neuroimaging Initiative data from 329 participants (207 cognitive normal, 94 MCI, 28 AD) with stable diagnosis and complete tau PET, structural MRI, and resting-state fMRI datasets. Across 10 Gordon (2016) networks, we tested whether network-specific tau was associated with cortical thickness, functional segregation, and persistence. Network persistence is defined as the continuous time a network maintains a positive co-activation pattern centroid value, and is a measure of temporal stability in network activity. Linear mixed-effects models tested whether local tau related to other network measures, adjusting for age and amyloid-β centiloid, with participant and network modeled as random intercepts.
In a mixed model examining main effects, tau was associated with cortical thickness (β=-0.163, t=-7.344, p=2.65e-13), age (β=-0.136, t=-3.411, p=7.25e-4), and centiloid (β=0.448, t=11.288, p<2.20e-16), but not segregation (β=-0.016, t=-1.191, p=0.234) or persistence (β=0.009, t=0.586, p=0.558). In a model including an interaction between thickness, segregation, and persistence, the tau-thickness relationship depended on both persistence (thickness x persistence: β=0.024, t=2.243, p=0.025) and segregation (thickness x segregation: β=-0.038, t=-3.579, p=3.50e-4), whereas the three-way interaction was not significant (p=0.815). Stronger tau-thickness coupling was associated with higher segregation, and although both higher segregation and higher persistence each relate to better cognition, the opposite-direction relationship was present for persistence. Persistence and segregation declined across diagnosis in the default mode and dorsal attention networks.
Together, our findings suggest that AD-related cortical atrophy is directly related to tau deposition in that tissue, whereas AD-related decreases in segregation and persistence are not directly driven by local tau. Instead, functional organization and temporal stability shape tau-atrophy coupling, supporting a multimodal model in which molecular, structural, and functional measures capture distinct aspects of network health.

Disclosures: A.T. Kahn: None. **D.S. Jin:** None. **J. Perucho:** None. **Y. Fang:** None. **K.M. Visscher:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.12/V3

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

Support: NIH Grant R01AG073133
NIH Grant R21AG089708
Additional funding and resources provided by the Moody Brain Health Institute at UTMB

Title: A novel non-toxic tau oligomer polymorph associated with cognitive resilience to AD-related neuropathology

Authors: *J. HARTMANN[1,2,3,4], M. MARCATTI[1,2], B. TUMURBAATAR[1,2], K. JOHNSON[1,3,5], Y. ZENG[1,3,5], W.-R. ZHANG[1,2,3], M.-A. MICCI[1,3,5], G. TAGLIALATELA[1,2,3]; [1]The Univ. of Texas Med. Br., Galveston, TX; [2]Mitchell Ctr. for Neurodegenerative Dis., UTMB Dept. of Neurol., Galveston, TX; [3]UTMB Moody Brain Hlth. Inst., Galveston, TX; [4]MD-PhD Combined Degree Program, UTMB Grad. Sch. of Biomed. Sci., Galveston, TX; [5]UTMB Dept. of Anesthesiol., Galveston, TX

Abstract: Alzheimer’s disease (AD) is characterized by amyloid-β plaques and neurofibrillary tau tangles, yet soluble tau oligomers are increasingly recognized as key mediators of synaptic dysfunction and neurodegeneration. However, individuals classified as non-demented with Alzheimer’s neuropathology (NDAN) maintain full cognitive function despite extensive pathological burden, suggesting the presence of protective tau states that resist toxicity. We propose that tau oligomers exist as structurally competing conformational states (or polymorphs) that determine neuronal vulnerability versus resilience. Human brain-derived tau oligomers (BDTOs) were isolated from postmortem hippocampi and characterized as AD- or NDAN-associated polymorphs. Here, we find that the NDAN-associated tau is conformationally distinct, less neurotoxic, and contains a mutation at S305R, just upstream of the amyloid domain. We prepared recombinant forms of these two tau polymorphs including both wild-type (AD-associated) and S305R (NDAN-associated), which we used for validation, recapitulating distinct functional phenotypes consistent with prior cellular and *in vivo* studies demonstrating reduced toxicity of NDAN-associated tau. Remarkably, co-assembly of S305R and wild-type tau monomers in a 1:10 molar ratio of S305R:wild-type biases oligomer formation toward a state resembling that of NDAN-associated tau. This supports a mechanistic model in which tau pathogenicity is governed by conformational competition within heterogeneous oligomer populations. To assess human neural relevance, we treated human induced pluripotent stem cell (iPSC)-derived cerebral organoids with tau oligomers, including recombinant and BDTO forms. Lactate dehydrogenase (LDH) assays revealed that pure AD-associated tau oligomers induced the highest cytotoxic response compared to pure NDAN-associated or co-assembled oligomers. In parallel, pilot microelectrode array recordings showed that AD-associated tau oligomers ablated the synchronized firing observed prior to treatment, indicating disruption of neuronal circuit function. Together, these findings support a model in which tau oligomer toxicity is

dynamically regulated by polymorphic state. This structural plasticity provides a mechanistic framework for resilience observed in NDAN individuals and identifies tau conformational state as a potential target for shifting disease-associated toxicity profiles.

Disclosures: J. Hartmann: None. **M. Marcatti:** None. **B. Tumurbaatar:** None. **K. Johnson:** None. **Y. Zeng:** None. **W. Zhang:** None. **M. Micci:** None. **G. Taglialatela:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.13/V4

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

Support: NIH Grant RF1 AG056130-02

Title: Evaluating the Impact of Trem2 H157Y on Microglial Function, Amyloid, and Tau Pathology

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Abstract: Background
TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) is a risk-associated gene for late-onset Alzheimer's disease (AD). The Trem2 H157Y variant, a risk allele located near the ectodomain shedding site, increases soluble Trem2 release, reduces full-length surface Trem2, and surprisingly reduces amyloid load in vivo. However, the mechanisms through which it contributes to AD risk, particularly in relation to tau pathology, remain unresolved.
Methods
To comprehensively evaluate the effects of Trem2 H157Y on amyloid and tau pathology, we established three experimental cohorts as follows. 1) Amyloid model: Trem2 H157Y (knock-in) mice were crossed with the APPSAA amyloid mouse model, and cohorts were analyzed at 4 and 8 months of age; 2) Tau model: A tauopathy model was generated by intracerebroventricular injection of AAV9-TauP301L at postnatal day 0 (P0) in Trem2 H157Y mice, which were harvested at 8 months of age for analysis; and 3) Combined amyloid and tau model: APPSAA/Trem2 H157Y mice received intracerebroventricular injection of AAV9-TauP301L at P0, and both amyloid and tau pathology were evaluated at 8 months of age.
Results
In the Tau-Trem2 H157Y model, behavioral analyses at 8 months revealed no significant differences between wild-type and Trem2 H157Y mice in motor function or associative memory. Neuropathological analyses showed no genotype-dependent differences in p-tau pathology in the cortex or hippocampus. Immunohistochemical analysis revealed no differences in PSD95 or Iba1 coverage, suggesting comparable synaptic integrity and microglial abundance between groups.

Similarly, CD68 density normalized to Iba1 coverage was unchanged. Biochemical analyses by Western blot suggested a reduction in the pTau/tTau ratio in the TBSX fraction of Trem2 H157Y mice despite the absence of overt histopathological differences. Characterization of the amyloid and combined amyloid-tau cohorts is currently ongoing.

Conclusion

The Trem2 H157Y variant does not substantially alter tau pathology, microglial activation, or behavioral outcomes in the AAV-TauP301L model at 8 months, although it may exert subtle effects on tau biochemistry. Together, findings from the amyloid-only, tau-only, and combined amyloid-tau cohorts will provide a more comprehensive understanding of how the H157Y variant influences AD-related pathology across distinct pathological contexts.

Disclosures: N. Takegami: None. **W. Qiao:** None. **G. Xhafkollari:** None. **Z. Li:** None. **L. Petrucelli:** None. **N. Zhao:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.14/V5

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

Support: NIH Grant R61AG094651

Title: Magnetogenetic activation of neurons modulates Tau pathology

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Abstract: In the Alzheimer’s disease (AD), tau pathology is key in its progression and cognitive decline. AD-vulnerable neurons exhibit hyperexcitability before AD onset, promoting tau accumulation, secretion, and propagation. Determining how neuronal activity regulates tau pathology may reveal critical mechanisms underlying the initiation and progression of AD. Here, we used FeRIC, a magnetogenetic platform developed in our laboratory that uses magnetic fields to activate ferritin-coupled TRPV channels, to increase neuronal activity and determine its impact on tau pathology. Using an *in vitro* model of tauopathy consisting of hippocampal neurons expressing the human tau P301L mutant, we assessed changes in tau phosphorylation and other pathological tau markers. Magnetic activation of neurons induced calcium spiking and action potential firing, leading to increased tau phosphorylation measured by western blotting and immunocytochemistry. The increase in tau phosphorylation occurred without changes in total tau levels (Tau5) but was accompanied by a reduction in non-phosphorylated tau (Tau1),

consistent with enhanced tau phosphorylation. Consistent with these effects, enhancing neuronal activity by blocking GABAergic transmission with bicuculline increased tau phosphorylation, whereas inhibiting glutamatergic transmission with AP5 and CNQX reduced tau phosphorylation. Together, these findings support a causal link between neuronal hyperactivity and tau-related pathological processes. Together, these findings demonstrate that magnetogenetic activation of neurons promotes tau pathology and provide the first proof-of-concept that magnetic neuromodulation can be used to investigate activity-dependent mechanisms of tau pathology. This work establishes a platform for the remote control of AD-vulnerable neuronal populations *in vivo*, enabling direct tests of the role of neuronal hyperactivity in the initiation and progression of AD and helping define the earliest activity-dependent pathological events underlying disease onset.

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Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.15/V6

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

Title: Same-Slide CellScape-to-GeoMx Workflow Enables Plaque and Tauopathy-Centric Profiling of Alzheimer’s Disease Microenvironments in Human Hippocampus

Authors: B. R. BERIGAN[1], *M. H. INGALLS[1], A. J. NORTHCUTT[1], L. WU[2], T. ORR[3], J. BEECHEM[2], O. BRAUBACH[1], M. E. ORR[3];
[1]Bruker Spatial Biol., Bruker, Saint Louis, MO; [2]Bruker Spatial Biol., Bruker, Seattle, WA; [3]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Amyloid plaques and tauopathy are defining features of Alzheimer’s disease (AD) and are associated with spatially organized microenvironments composed of distinct neuronal and glial cell states. Defining the cellular composition of such niches remains challenging, as the deep molecular profiling that resolves them, such as the GeoMx® Digital Spatial Profiler (DSP), delivers valuable insight when its regions of interest (ROIs) are guided by whole-tissue, high-plex, single-cell phenotypic context beyond standard morphology marker-driven approaches. To address this, we developed a same-slide cross-platform workflow that uses phenotypic results from the CellScape™ XR platform to guide ROI selection for high-plex molecular profiling with GeoMx DSP. The CellScape XR platform was used to generate single-cell maps of protein expression using a 44-plex antibody panel with a DNA counterstain, revealing comprehensive tissue architecture, cellular composition, and disease-associated phenotypes across a human FFPE hippocampal section. This approach resolved the spatial organization of neuronal subtypes, glial activation states, synaptic integrity, and protein aggregation across plaque-associated microenvironments with or without tau.

Whole-section mapping from the CellScape XR assay revealed distinct disease-associated niches defined by differential enrichment of activated microglia, heterogeneous neuronal populations, and localized synaptic and proteostatic alterations. The CellScape XR-derived maps were then used to guide same-slide GeoMx DSP ultra-high-plex profiling (>1,000 targets) to resolve molecular programs defining each niche. Shared morphology markers from the CellScape XR assay enabled spatial registration and precise targeting of tau +/- plaque cores, peri-plaque regions, and distal tissue, enabling biology-driven rather than morphology-based ROI placement. These ROIs linked cellular composition with deep molecular signatures of disease-associated microenvironments, revealing unique microglial phenotypes associated with amyloid plaque and tau pathology.
Our data demonstrate that this workflow enables unbiased, biology-driven ROI selection, pairing whole-section single-cell phenotyping with deep molecular profiling, leading to the identification of novel phenotypes in human Alzheimer's disease.

Disclosures: B.R. Berigan: None. **M.H. Ingalls:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. **A.J. Northcutt:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. **L. Wu:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. **T. Orr:** None. **J. Beechem:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. **O. Braubach:** A. Employment/Salary (full or part-time):; Bruker Spatial Biology. **M.E. Orr:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.16/V7

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

Support: 1R21AG089708
1R01AG073133
Moody Brain Health Institute

Title: A Novel Oligomeric Tau Polymorph May Predominate within the Resilient AD Cerebellum

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Abstract: Alzheimer's disease (AD) is the current leading causes of dementia in the United States, as well as one of the fastest growing. Current therapeutics are palliative and largely ineffective, representing an unmet need. Misfolded tau is a major histopathological hallmark of AD, and its propagation through the brain correlates strongly with disease progression. Some brain regions, particularly primary sensory cortices, demonstrate remarkably delayed tau pathology given the otherwise highly predictable, connectivity-driven pattern of spread. Further,

the cerebellum remains largely unaffected, even in advanced cases, implying some intrinsic mechanism of "resistance" in these structures, investigation of which stands to inform future therapeutic approaches. Recent data from our group has demonstrated the existence of an AD-associated polymorph of oligomeric tau with significantly reduced toxicity in asymptomatic individuals, opening the door for other previously unknown, variably-toxic oligomers which have never been investigated within the symptomatic AD brain. Preliminary data examining post-mortem AD cerebellar cortical tissue (n = 3) suggests at least one such morphological variant exists in late-stage AD patients (Braak stage 6). The functional relevance of such tau polymorph in the cerebellum is supported by synaptic tau interactomic data we obtained via LC-MS indicating differential engagement with vesicular membrane, proteosomal, and post-synaptic density-associated proteins as compared to the tau interactome of vulnerable areas such as hippocampus. These data suggest that cerebellar resilience to AD pathology may involve the local presence of a less toxic tau polymorph species. Further investigation may provide insight into a targetable mechanism for guiding tau aggregation towards less toxic forms in early- and mid-stage Alzheimer's patients. Supported by NIH/NIA grant 1R21AG089708 and 1R01AG073133 and the Moody Brain Health Institute.

Disclosures: R.A. Schuetze: None. **G. Taglialatela:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.17/V8

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

Support: US Department of Education GAANN Fellowship P200A240048

Title: The Unfolded Protein Response in Astrocyte-Like Glial Cells: Implications for Tau Propagation and Short-Term Memory Deficits in Caenorhabditis elegans

Authors: *K. MORALES CAJIGAS[1], D. L. RAMOS-ORTOLAZA[2];
[2]Dept. of Natural Sci., [1]Pontifical Catholic Univ. of Puerto Rico, Ponce, PR

Abstract: Tau pathology is a major driver of cognitive decline in several neurodegenerative disorders, including Alzheimer's Disease. Astrocytes have been recognized as being involved in the propagation of pathogenic tau, potentially contributing to memory impairments observed in these disorders. Although specific mechanisms remain unknown, a key pathway thought to contribute to astrocytic dysfunction and potentially tau propagation is the unfolded protein response (UPR), a protective endoplasmic reticulum (ER) stress pathway activated by disruptions in ER calcium homeostasis and accumulation of misfolded proteins. While acute UPR activation helps restore cellular homeostasis, chronic activation by pathogenic tau may shift this response from adaptive to maladaptive, potentially contributing to astrocytic dysfunction and tau propagation. However, the extent to which other factors can exacerbate this tau-mediated

maladaptive response in astrocytes is currently unknown. Our aim is to investigate whether chronic activation of the astrocytic UPR promotes calcium-dependent tau propagation and contributes to short-term memory deficits in a *Caenorhabditis elegans* model of tauopathy. To achieve this, ER stress will be induced using thapsigargin in the EVL1644 *C. elegans* strain, which expresses human P301S tau fused to GFP under the pan-neuronal *rgef-1* promoter. Following chronic ER stress, tau propagation will be assessed by fluorescence imaging, while short-term memory will be evaluated using a chemotaxis-based learning assay. To confirm astrocytic UPR activation, expression of UPR-associated genes like xbp-1s and hsp-4 will be measured by qPCR in the EVL1644 strain and a reference strain, AGD1724, which overexpresses the xbp1-s in astrocyte-like CEPsh glia. Finally, to assess whether calcium contributes to tau propagation and associated memory deficits, animals will be exposed to the calcium chelator EGTA following chronic ER stress induction. Our results showed that EVL1644 animals formed tau aggregates throughout their nervous system. Upon assessment, animals from this strain showed deficits in short-term memory compared to wild-type controls. We expect that chronic ER stress will increase UPR activation, promoting tau propagation and short-term memory deficits. We further anticipate that calcium chelation with EGTA will attenuate these effects, supporting calcium-mediated mechanisms of tau spread. These results will provide insight into the potential role of astrocytes in tau propagation which will allow to identify glial pathways as potential therapeutic targets for tauopathies.

Disclosures: K. Morales Cajigas: None. **D.L. Ramos-Ortolaza:** None.

Poster

PSTR261: Alzheimer's Disease: Tau Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR261.18/V9

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

Support: T32 Award 1T32GM152779-01
T32 Award 5T32NS007431-27

Title: Mechanisms and Consequences of Primary Cilia Dysfunction in Alzheimer’s Disease

Authors: *M. G. MURCAR[1], H. PRUITT[2], T. J. COHEN[3], S. S. KHAN[4];
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Abstract: Alzheimer’s Disease (AD) is an adult-onset neurodegenerative disease that affects almost 7 million senior Americans, and the prevalence is expected to double by 2060. Preliminary work in our lab has revealed primary cilia dysfunction in postmortem brain tissue of human AD patients. Cilia are microtubule-based organelles that extend from the cell body of neurons and regulate neuromodulatory signaling cascades, such as the sonic hedgehog pathway.

There is a gap in knowledge on the mechanisms and functional consequences of cilia changes in AD. We hypothesize that tau pathology is driving the ciliation changes that we see in AD. We have found that 6.5-7.5 month old Mapt knock-in mice have decreased cilia length in the mPFC and decreased ciliation frequency in the hilus. Introducing aggregate-prone tau mutants to retinal pigment epithelium cells resulted in loss of primary cilia. Finally, we are investigating the consequences of tau on cilia function and propose that tau interferes with activation of the sonic hedgehog pathway. Understanding the mechanisms of tau pathology are crucial for identifying targets for therapeutic intervention in this debilitating neurodegenerative disorder.

Disclosures: M.G. Murcar: None. **H. Pruitt:** None. **T.J. Cohen:** None. **S.S. Khan:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.01/V10

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

Support: NIA Grant P01AG026572
NIA Grant T32AG082631
Center for Innovation in Brain Science

Title: Reverse-translation of real-world menopausal hormone therapy data with a humanized APP/APOE Alzheimer's disease risk mouse model

Authors: *M. BANTUGAN[1,2], S. RAGSDALE[1,2], A. K. PARKER[1], F. VITALI[1,3], T. WANG[1,3], R. D. BRINTON[1,3,4];
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Abstract: Alzheimer’s disease (AD) is a major public health challenge that disproportionately affects women, who account for nearly two-thirds of diagnosed cases. Despite this disparity, sex-specific risk factors and therapeutic strategies remain underexplored. The menopausal transition, characterized by a decline in ovarian estrogen production, has been implicated as a critical window of vulnerability for AD risk. Menopausal hormone therapies (MHTs) have therefore emerged as promising candidates for mitigating AD development. However, the translatability of the most commonly prescribed MHT to mechanistic outcomes in a preclinical genetic risk model of AD remains poorly defined.
We employed a reverse-translational framework integrating real-world health insurance data with experimental studies in a genetic mouse model of AD-risk. The US-based Mariner claim database was utilized to identify women prescribed MHTs and characterized therapy formulation and age at initiation. Sensitivity analyses evaluated associations between MHT class, initiation timing, and AD incidence. Guided by population-level findings indicating estrogen-based therapies as the predominant MHT class, we conducted preclinical studies in 14-month-old

female humanized *APP*/*APOE* mice. Animals received subcutaneous 60-day slow-release 17β-estradiol (0.09 mg/pellet) for 30 days or sham treatment. To model clinically relevant initiation windows, both regular and irregular cyclers were randomized to treatment or sham. Metabolic and physiological outcomes commonly disrupted in both AD and menopause, including fasting blood glucose and ketones, body composition (assessed by EchoMRI), and cycling status, were assessed before tissue collection.
Medical informatics analyses of insurance claims data revealed distinct AD risk profiles across MHT classes, with earlier initiation of therapy (before age 60) associated with lower AD odds compared to later initiation. Estrogen-based therapies represented the predominant class of prescribed MHTs, with estrogen-progestogen combined representing 12% of MHT users. In parallel, preclinical studies suggested that estrogenic interventions modulate biological pathways implicated in AD and menopause, including reduced body weight by 34% ($p<0.05$). Other assessed outcomes reflective of menopausal pathway changes did not differ by treatment.
By correlating population-level patterns of MHT use with targeted interventions in a genetic AD risk model, this work informs ongoing studies aimed at elucidating the biological pathways implicated in the most translationally relevant window of elevated AD risk in women.

Disclosures: M. Bantugan: None. **S. Ragsdale:** None. **A.K. Parker:** None. **F. Vitali:** None. **T. Wang:** None. **R.D. Brinton:** Other; President/Founder of NeuTherapeutics, LLC.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.02/V11

Topic:

Support: NIA Grant T32AG061897
NIA Grant R37AG053589
NIA Grant P01AG026572
Center for Innovation in Brain Science

Title: Single-nuclei transcriptomics identifies cell-type-specific estrogen-dependent pathway alterations relevant to Alzheimer’s disease in female rat hippocampus

Authors: *J. W. MCLEAN[1,2], T. WANG[1], R. D. BRINTON[1,3,4];
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Abstract: Estrogen regulates metabolic, immune, and neuronal function in the female brain. Reduction in estrogen levels during menopause impacts processes associated with Alzheimer’s disease (AD) pathogenesis, including glucose utilization, mitochondrial function, and neuroinflammation, likely contributing to the doubled female lifetime risk for AD. However, the cell-type-specific response to estrogen deficiency in the hippocampus, which is critically affected

in AD, is insufficiently understood.
To elucidate hippocampal cells and pathways affected by estrogen loss, 5-month-old female Sprague Dawley rats were assigned to sham ovariectomized (SHAM), ovariectomized plus vehicle (OVX), or OVX with 17β-estradiol (OVX+E2) conditions and sacrificed 5 weeks post-surgery. Single nuclei were isolated from dorsal hippocampus, pooled across two biological replicates per group, and processed using the 10X Genomics Chromium Single Cell 3' platform. Libraries were sequenced on an Illumina NovaSeq6000, and downstream analyses were conducted using CellRanger v9.0.1 and R v4.5.2. Following quality control filtering out nuclei with >5% mitochondrial reads, canonical marker genes were used to annotate major brain cell types. Cell-type proportion tests, differential expression, pathway-level analyses, and CellChat ligand-receptor (LR) interaction tests were performed across conditions and cell types.
Relative to SHAM, OVX shifted cellular composition toward reduced excitatory (Exc) and inhibitory (Inh) neuron and elevated oligodendrocyte (Olig) proportions. Pathway analysis of DEG's between OVX and SHAM indicated significantly enriched KEGG pathways associated with neurodegeneration (Exc) and inflammation (Exc, Inh, Olig), while metabolic pathways were downregulated (Olig). Neuroactive ligand signaling was also significantly diminished in multiple OVX cell types, prompting an LR interaction analysis using CellChat. This indicated a specific deficit in predicted OVX Exc communication toward both Exc and Inh along with elevated microglial signaling with Inh and Olig. OVX+E2 partially mitigated several OVX-induced phenotypes, including cell-type composition shifts, Inh inflammatory response, and both Exc-Exc and Exc-Inh communication predicted via CellChat.
These findings extend previous reports connecting estrogen loss to AD risk by identifying cell-type-specific metabolic, inflammatory, and cell signaling phenotypes induced by OVX and partially moderated by E2 replacement. Ongoing analyses will further resolve cell-type-specific ligand-receptor interactions underlying estrogen-dependent vulnerability to AD.

Disclosures: J.W. McLean: None. **T. Wang:** None. **R.D. Brinton:** Other; President/Founder of NeuTherapeutics, LLC.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.03/V12

Topic:

Support: National Institute on Aging grant AZ-TRADD T32AG061897
National Institute on Aging grant P01AG026572
Center for Innovation in Brain Science

Title: Plasma Proteomic Signatures of Alzheimer's Disease Risk Are Differentially Shaped by Menopausal Hormone Therapy Formulation, Initiation Timing, and APOE Genotype in Postmenopausal Women

Authors: *S. M. RAGSDALE[1,2], G. HOLMGREN[2], F. VITALI[2,3,4], R. D. BRINTON[2,3,5]; [1]Neurosci. Grad. Interdisciplinary Program, [2]Ctr. for Innovation in Brain Science, Univ. of Arizona Hlth. Sci., [3]Dept. of Neurology, Univ. of Arizona Col. of Med., [4]Ctr. for Biomed. Informatics and Biostatistics, [5]Dept. of Pharmacology, Univ. of Arizona Col. of Med., Univ. of Arizona, Tucson, AZ

Abstract: Alzheimer's disease (AD) disproportionately affects women, with nearly two-thirds of cases occurring in females and incidence accelerating after menopause. The APOE4 allele is the strongest genetic risk factor for late-onset AD, conferring 3-12-fold increased risk and is associated with reprogrammed metabolic and inflammatory networks in postmenopausal women. While the menopausal transition can be a critical neurobiological vulnerability window, the impact of menopausal hormone therapy (MHT) timing and formulation on AD risk remains unresolved.

We investigated the impact of MHT timing, “early” (<5 years post-menopause) vs “late” (>5 years), and formulation (estrogen-only vs combined estrogen + progestogen) may differentially modulate AD-relevant biology depending on APOE genotype. Resolving this three-way interaction is essential for precision AD prevention.

Using UK Biobank plasma proteomic data from 4,590 postmenopausal women, we examined protein level differences stratified by MHT formulation, initiation timing, and APOE genotype. Participants were stratified into 5 MHT groups (Combined + Early, Combined + Late, Estrogen + Early, Estrogen + Late, No MHT) and three genotype strata (APOE2 carriers, E3/E3 homozygotes, APOE4 carriers). Early initiators began MHT 2.5-2.8 years post-menopause versus 10.8-13.2 years for late initiators. APOE4 carriers demonstrated approximately 7-fold higher AD incidence compared to E3/E3 homozygotes ($p<0.001$), consistent with established genetic risk effects. Differential protein expression and pathway enrichment analyses identified proteins involved in inflammatory, metabolic, and neurodegenerative pathways. Principal component analysis indicated that proteomic differences are distributed across multiple proteins (PC1=17.4%, PC2=5.6%), supporting pathway-level rather than single-biomarker characterization of these signatures.

These findings suggest that MHT formulation and timing produce differential proteomic signatures that vary by APOE genotype, indicating that hormone therapy may engage genotype-dependent molecular programs rather than uniformly protecting against or exacerbating AD-related biology. This work identifies candidate biological modifiers of postmenopausal AD risk and provides a basis for developing appropriately timed genotype-informed hormone therapy strategies, addressing the critical need for sex-specific AD prevention.

Disclosures: S.M. Ragsdale: None. **G. Holmgren:** None. **F. Vitali:** None. **R.D. Brinton:** Other; President/Founder of NeuTherapeutics, LLC.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.04/V13

Topic:

Title: Ai driven discovery of brain penetrant Sting inhibitors for treatment of Alzheimer's disease: An integrated LLM-guided design and experimentally validated ADMET prediction framework

Authors: *N. ZHI;
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Abstract: The STING pathway has emerged as a critical regulator of innate immune activation and neuroinflammation, making it a promising therapeutic target for Alzheimer's disease (AD) [1,2]. Aberrant STING signaling has been implicated in chronic neuroinflammatory responses, microglial activation, and downstream neuronal dysfunction, all of which contribute to AD progression [2,3]. However, the discovery of brain-penetrant and pharmacologically optimized STING inhibitors remains challenging due to stringent blood-brain barrier (BBB) constraints and complex structure-activity relationships. In this study, we propose an integrated AI-driven drug discovery and experimental validation framework for the development of novel STING inhibitors for AD therapy. We combine large language model (LLM)-guided molecular design with graph-based deep learning models and experimentally trained quantitative structure-property relationship (QSPR) models to enable rapid scaffold generation and optimization. Key ADMET properties, including BBB permeability, metabolic stability, solubility, and toxicity liabilities, are predicted prior to synthesis using models trained on experimentally validated datasets. Notably, BBB penetration is evaluated using a probabilistic scoring system, where lower probability scores indicate higher likelihood of brain penetration, enabling early prioritization of CNS-active candidates. Selected compounds are subsequently synthesized and experimentally validated through iterative medicinal chemistry cycles, including target engagement assays, cellular STING activation/inhibition assays, and neuroinflammation-related functional readouts. The integration of computational prediction with wet-lab validation establishes a closed-loop optimization platform that accelerates lead identification and refinement. Importantly, this framework enables rational mapping between molecular structure, predicted BBB permeability, and experimental CNS activity, providing mechanistic insights for scaffold optimization. This AI- and experiment-integrated pipeline offers a powerful strategy to accelerate the discovery of brain-penetrant STING inhibitors and holds significant potential for the development of disease-modifying therapies for Alzheimer's disease.Reference:[1] Decout, A., et al. (2017). The STING pathway in health and disease. *Nature Reviews Immunology*.[2] Barbeau, J. O., et al. (2023). Innate immune signaling and neurodegeneration: STING in Alzheimer's disease. *Nature Neuroscience*.[3] Zhao, W., et al. (2022). Neuroinflammation and microglial activation in Alzheimer's disease. *Neuron*.

Disclosures: N. Zhi: None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.05/V14

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

Support: NIH R01AG055549 (to ET)
UG3/UH3NS113776 (to ET)
U19 AG069701 (to TK)
Alzheimer's Association Research Fellowship grant 23AARF-1027342 (to TKON)

Title: Weak mitochondrial complex I inhibitors restore glucose metabolism and bioenergetics in models of Alzheimer's disease

Authors: *T. NGUYEN[1], S. TRUSHIN[1], T. KOVALENKO[1], M. OSTROOT[1], O. RAMÍREZ MOLINA, Sr.[4], H. LEE[1], T. NAMBARA[5], T. KANEKIYO[5], P. BALONI[6], E. TRUSHINA[2,3]; [1]Neurol., [2]Dept. of Neurol., [3]Mol. Pharmacol. and Exptl. Therapeut., Mayo Clin., Rochester, MN; [4]Univ. de Concepción, Concepción, Chile; [5]Neurosci., Mayo Clin. Jacksonville, Jacksonville, FL; [6]Sch. of Hlth. Sci., Purdue Univ., West Lafayette, IN

Abstract: There is an urgent need for therapies that target early molecular mechanisms driving Alzheimer's disease (AD) progression. Synaptic loss, tightly linked to cognitive decline in AD, is driven by early impairments in glucose uptake and utilization and by reduced energy homeostasis. We demonstrated that the neuroprotective tool compound CP2 binds directly to the quinone site of mitochondrial complex I (mtCI) and acts as a weak inhibitor, inducing transient energetic stress that activates AMPK and downstream adaptive stress responses. The resulting metabolic reprogramming enhances glucose uptake and utilization, stimulates mitochondrial biogenesis, and restores synaptic and metabolic function in multiple AD mouse models. Using rational drug design and structure-activity relationship studies, we developed selective mtCI inhibitors with improved drug-like properties, culminating in the clinically optimized lead compound C273. This study aimed to elucidate the molecular mechanisms by which mtCI inhibitors improve glucose metabolism and mitochondrial bioenergetics in AD models.SH-SY5Y neuroblastoma cells expressing mutant human APP (APPswe) and human iPSC-derived cerebral organoids from late-onset AD (APOE4/4) patients were used throughout. Glycolysis, mitochondrial respiration, and fatty acid β-oxidation were measured with a Seahorse Analyzer; glucose transporter expression and localization were assessed by flow cytometry and immunofluorescence; protein expression was analyzed by Western blot and ELISA; glucose uptake was quantified using the Glucose Uptake-Glo assay; metabolic flux was evaluated using 13C-labeled glucose with targeted metabolomics; and ChIP-seq was performed to analyze pathway enrichment.APPswe cells exhibited elevated Aβ40 levels, impaired mitochondrial respiration and glycolysis, reduced glucose uptake, and increased reliance on fatty acid oxidation and amino acid metabolism. At physiologically relevant concentrations, mtCI inhibitors improved mitochondrial bioenergetics, enhanced glucose uptake, and promoted GLUT3 and GLUT4 translocation to the plasma membrane. Increased glucose utilization was associated with reduced p-PDH and enhanced pyruvate-to-acetyl-CoA conversion, fueling the TCA cycle and generating signaling metabolites critical for AMPK-dependent gene regulation. In LOAD patient-derived cerebral organoids, mtCI inhibitors activated an AMPK-dependent adaptive stress response and reduced Aβ and pTau levels. These data support the development of weak

mtCI inhibitors targeting early metabolic dysfunction as a disease-modifying therapeutic strategy for AD.

Disclosures: T. Nguyen: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one patent applications owned by Mayo Foundation for Medical Education and Research. **S. Trushin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **T. Kovalenko:** None. **M. Ostroot:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **O. Ramírez Molina:** None. **H. Lee:** None. **T. Nambara:** None. **T. Kanekiyo:** None. **P. Baloni:** None. **E. Trushina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.06/V15

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

Title: Neurotrophic Factor-α1/Carboxypeptidase E interacts with purinergic receptor P2Y4 to mediate neuroprotection in mouse neurons

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Abstract: Neurotrophic Factor-α1/Carboxypeptidase E (NF-α1/CPE) is a neuroprotective protein that promotes neuronal survival under conditions of oxidative and excitotoxic stress. Our previous studies demonstrated that NF-α1/CPE interacts with the serotonin receptor human 5-HTR1E to activate β-arrestin-dependent pro-survival signaling. To identify additional receptor partners that may mediate the neuroprotective actions of NF-α1/CPE, we screened a G protein-coupled receptor (GPCR) library (GPCRome) comprising approximately 320 GPCRs. This screening identified more than ten GPCRs that were activated in response to NF-α1/CPE, suggesting that NF-α1/CPE may function through multiple receptor-mediated pathways. Among the candidate receptors, the purinergic receptor P2RY4 emerged as a promising target for further investigation. Using a GPCR Tango assay, we observed activation of P2RY4 signaling in response to NF-α1/CPE. In addition, characterization of P2Y4 receptor expression revealed its distribution across multiple cell lines and distinct mouse brain regions, supporting a potential role in central nervous system function. Functional studies using lactate dehydrogenase (LDH)

cytotoxicity assays provided preliminary evidence that NF-α1/CPE-P2RY4 signaling contributes to cellular protection against oxidative stress. Together, these findings suggest that NF-α1/CPE interacts with P2RY4 to mediate purinergic receptor signaling and contribute to the neuroprotective actions of NF-α1/CPE.

Disclosures: A. Anandan: None. **X. yang:** None. **Y. Loh:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.07/V16

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

Support: AG086510
AG088226

Title: Elucidating the role of mitovesicles, mitochondria-derived extracellular vesicles, in Alzheimer's disease and Down syndrome

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Abstract: INTRODUCTION: Extracellular vesicles (EVs) are membrane-bound vesicles released into the extracellular space that are critical for maintaining cell homeostasis. Our group has previously described the isolation and characterization of a novel type of EVs derived from mitochondria, named mitovesicles, with unique characteristics when compared to other EVs. We previously reported that mitovesicle number and content are altered in the presence of mitochondrial dysfunction, suggesting a role for mitovesicle secretion as a novel mitochondrial quality control mechanism removing damaged mitochondrial components from a cell. In this study, we compared the generation, content, and secretion of mitovesicles and other EVs in the brain of mouse models of Down Syndrome (DS) and β-amyloidosis, Alzheimer’s disease-relevant models with mitochondrial dysfunction. In addition, we studied the effects of mitovesicles on synaptic function, positing that mitovesicles derived from these models impair memory consolidation when compared to controls. METHODS: EVs were isolated from the brain of Ts2 (DS) and $APP^{NL\text{-}F/NL\text{-}F}$ (β-amyloidosis) mice together with age-matched controls. EVs were fractionated into different subpopulations, including mitovesicles, following a protocol developed in our lab (D’Acunzo et al, 2022). EVs were characterized by electron microscopy, nanoparticle tracking analysis, Western blotting, and a monoamine oxidase enzymatic assay. Wild-type hippocampal slices were perfused with artificial cerebrospinal fluid containing these

brain-derived mitovesicles, pretreated with or without monoamine oxidase (MAO) inhibitors. Long-term potentiation (LTP) was assessed. RESULTS: Alterations in mitovesicle secretion, number, and content were found in brains of both DS and β-amyloidosis murine models when compared to controls, suggesting a mitovesicle contribution to pathology. Administration of physiological levels of these mitovesicles impaired LTP, with the DS and $APP^{NL-F/NL-F}$-derived mitovesicles having a significantly greater effect than those isolated from controls. Inhibition of MAO-B activity eliminated the ability of mitovesicles to alter LTP. CONCLUSIONS: Mitovesicle secretion is a novel hotspot within mitochondrial quality control whereby cells may remove damaged mitochondrial components and restore mitochondrial homeostasis. Findings from this work contribute to the understanding of mitochondrial dysfunction and the physiological function of mitovesicles while giving new insights into the role of mitovesicles in DS and Alzheimer's disease.

Disclosures: M. Valle: None. **E.K. Argyrousi:** None. **O. Arancio:** None. **P. D'Acunzo:** None. **P.M. Mathews:** None. **E. Levy:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.08/V17

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

Support: NIH RO1 grant, R01 AG083947-01

Title: Mitochondrial Targeted Photobiomodulation Mitigates Tacrine-Induced and Broad Drug-Induced Toxicity

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Abstract: Introduction: Drug-induced hepatotoxicity remains a major clinical limitation, largely driven by mitochondrial dysfunction and oxidative stress. Tacrine, a former acetylcholinesterase inhibitor for Alzheimer disease, induces liver injury by disrupting mitochondrial homeostasis. Photobiomodulation (PBM) is a noninvasive approach with translational potential, yet its role in drug-induced toxicity remains unclear. This study examines whether PBM mitigates tacrine- and multidrug-induced mitochondrial dysfunction.Methods: HepG2 cells were treated with tacrine (100 μM) and exposed to PBM (655 nm, continuous wave, 8 J/cm², 4.7 min) 2 h post-treatment. Mitochondrial function was assessed by ATP production, mitochondrial membrane potential (ΔΨm), and reactive oxygen species (ROS).Results: PBM markedly improved mitochondrial function in tacrine-exposed cells, as shown by increased ATP, restored ΔΨm, and reduced mitochondrial ROS. It also enhanced cell viability, indicating protection against drug-induced

injury. Similar protective effects were observed with other mitochondria-disrupting agents (amiodarone hydrochloride, chloramphenicol, diclofenac, sodium valproate, and fialuridine), suggesting broader applicability beyond tacrine.Conclusions: These findings highlight PBM as a promising mitochondrial targeted therapeutic strategy and support its broader potential in alleviating drug induced toxicity.

Disclosures: N. Yang: None. **J. zhang:** None. **X. zong:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.09/V18

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

Support: CIHR PJT191806
NIH R01AG084681

Title: The impact of Ascl1SA6-mediated astrocyte-to-neuron reprogramming on hippocampal circuit functionality in the Fischer 344 Transgenic Rat Model of Alzheimer's Disease

Authors: K. CHEN[1], ***J. HE**[5], M. KOLETAR[2], M. HILL[1], J. RIBEIRO[1], J. MCLAURIN[3,6], B. STEFANOVIC[4,7];
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Abstract: Alzheimer’s disease (AD) is a devastating neurodegenerative disorder that progressively impairs cognitive function and ultimately results in death. To date, no treatment can halt or reverse disease progression, highlighting the urgent need for new therapeutic strategies. Neuronal loss, particularly the early vulnerability of GABAergic interneurons, is a key pathological feature of AD and leads to circuit dysfunction and cognitive decline. Therefore, therapeutic strategies that promote interneuron replacement or regeneration may provide a promising avenue for restoring brain circuits function in AD. Although endogenous neurogenesis and neuronal replacement are limited in the adult brain, direct reprogramming using proneural transcription factors (TF) may help overcome this limitation by converting glial cells into induced neurons in situ. Ascl1 is one such TF and has been characterized as a driver of GABAergic interneuron induction from astrocytes. Astrocytes are abundant in the brain and become reactive and proliferative in the context of AD, making them a cellular reservoir for regenerative intervention. In this study, six serine phospho-acceptor sites were mutated in Ascl1 to alanines (Ascl1SA6) to prevent phosphorylation by proline-directed serine/threonine kinases. We then employed ultra-high-density electrophysiological Neuropixels recordings to investigate whether and how AAV2/5-GFAP-Ascl1SA6 -mediated astrocyte-to-neuron reprogramming influences hippocampal circuit activity in 15-month-old Fischer 344 transgenic AD rats. Our

preliminary findings indicate that Ascl1SA6-treated transgenic rats exhibit reduced evoked local field potentials when compared to control transgenic rats, suggesting enhanced inhibitory tone and reduced neuronal hyperexcitability. This project will evaluate the therapeutic potential of neuronal reprogramming strategies aimed at restoring GABAergic interneuron function and improving cognitive outcomes in AD.

Disclosures: K. Chen: None. **J. He:** None. **M. Koletar:** None. **M. Hill:** None. **J. Ribeiro:** None. **J. McLaurin:** None. **B. Stefanovic:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.10/V19

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

Support: U01 AG032969
R01 AG067598
R01 AG074004
R01 AG072599
RF1 AG071805
U01 AG032969
P30 CA008748

Title: Epichaperome Prevalence Across the Alzheimer’s Disease Continuum and its Relationship to Cognitive and Neuropathologic Measures

Authors: S. D. GINSBERG[1], A. RODINA[4], T. ROYCHOWDHURY[5], S. BAY[6], S. SHARMA[4], A. LABUZA[7], A. STANISAVLJEVIC[2], C. S. DIGWAL[5], P. PANCHAL[5], M. J. ALLDRED[3], P. E. FRASER[8], M. ISHII[9], O. ARANCIO[10], D. A. BENNETT[11], *G. CHIOSIS[5]; [1]Ctr. for Dementia Res., Nathan Kline Inst., Orangeburg, NY; [2]Biopharmaceutical Scienes, Nathan Kline Inst., Ridgewood, NY; [3]Nathan Kline Inst., Orangeburg, NY; [4]Mem. Sloan Kettering Cancer Ctr., New York, NY; [5]Mem. Sloan Kettering Cancer Ctr., NEW YORK, NY; [6]CHEMICAL BIOLOGY, Sloan-Kettering Inst., NEW YORK, NY; [7]Psychology, Nathan S Kline Inst., Nanuet, NY; [8]Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada; [9]Neurol., UT Southwestern, Dallas, TX; [10]taub Inst., Columbia Univ., New York, NY; [11]Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL

Abstract: Alzheimer’s disease (AD) is defined neuropathologically by hallmark lesions amyloid-β plaques and tau-containing neurofibrillary tangles, along with synaptic loss and inflammation. These pathological changes do not fully address clinical heterogeneity nor the molecular basis of cognitive decline. Epichaperomes are stable, disease-associated assemblies of chaperones and co-chaperones that remodel protein interaction networks and have been implicated in proteome dysfunction, synaptic failure, and neurodegenerative disease. Whether

epichaperomes are prevalent across the human AD continuum and how they relate to cognitive and neuropathologic measures remains incompletely understood. We quantified epichaperome levels in >100 postmortem human frontal cortex (Brodmann area 9) tissue from individuals spanning no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD from two well-powered cohorts. Epichaperomes were measured using native gel-based biochemical detection of high-molecular-weight assemblies, enabling assessment of assembly-state remodeling rather than protein abundance. Epichaperome signal was evaluated in relation to clinical diagnosis, cognitive performance, and canonical AD neuropathologic measures. Epichaperomes were low or largely absent in NCI cases but were elevated across the AD continuum, including in MCI and AD brains. A substantial fraction of MCI and AD cases showed high epichaperome signal relative to the reference age-matched NCI specimens, indicating that epichaperome remodeling is a common feature of symptomatic AD spectrum disease. Higher epichaperome levels were associated with worse cognitive performance, supporting a relationship between epichaperome formation and functional decline. In contrast, epichaperome signal did not correlate with amyloid or tau burden, suggesting that epichaperomes capture a distinct layer of disease-associated molecular dysfunction. These findings establish epichaperome remodeling as a prevalent feature of human AD spectrum brain tissue and support a relationship with cognitive decline. Broadly, these data suggest epichaperomes provide key information about proteome-network dysfunction that is not fully captured by conventional amyloid and tau pathology, highlighting their potential value as markers of disease-associated functional vulnerability in AD.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.11/V20

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

Support: NCInnovation grant NCI-127
NIH grant T34-GM149434-01A1

Title: Development of small-molecule autophagy-lysosomal enhancers as a novel treatment modality for reducing multiple types of pathogenic proteins that contribute to Alzheimer’s disease.

Authors: *M. R. CHEBAHTAH[1], M. C. PAIT[1], G. KIPSISIN[1,2], N. L. PACHECO[3], C. OXENDINE[4], M. F. ALMEIDA[5,1], B. A. BAHR[1];
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Abstract: Aiming to develop an effective treatment for reducing the proteinopathy and associated synaptopathy of Alzheimer's disease (AD), we elucidated lysosomal compensatory responses in the brain and avenues for the pharmacological modulation of the autophagy-lysosomal pathway (ALP) to i) improve clearance of pathogenic material and ii) restore neuronal homeostasis needed for cognitive function. The ALP is essential for proteostasis, and its dysfunction plays a role in AD pathology (Wang et al. 2018 *Cur Op Neurobiol* 48:52; Almeida et al. 2024 *Ageing Res Rev* 93:102162; Lane-Donovan et al. 2025 *Prog Neurobiol* 255:102854; Ackley et al. 2026 *Mol Neurodegen Adv* 2:10). The ALP modulation hypothesis for treating AD multiproteinopathy stems from reports that such a strategy enhances clearance of Aβ42 (found in 100% of AD cases), pTau (found in 100% of AD), and α-synuclein (found in 50% of AD). Our drug discovery efforts have developed several series of small molecules that enhance the ALP (U.S. Patents 8,163,953 & 10,702,571; PCT/US2025/050375 app. and associated U.S. filing), with screening conducted in rat hippocampal slice cultures. Several members of the novel series produced 2-4-fold increases in the active form of cathepsin B (CatB), a lysosomal hydrolase we and others found to degrade Aβ42. Stereoselectivity was found for the CatB positive modulation, the lead candidates exhibited EC50s of 0.8 - 2.4 μM, and synaptic markers were unchanged or modestly increased. Compound formulation was determined for Maximum Tolerated Dose studies (15-100 mg/kg/d, ip), and compounds were well tolerated across all dosages (no animal welfare issues observed after 14 days). Efficacy testing then assessed an age-related memory deficit (exploratory habituation) in mice 13-14 months of age. After 14 daily treatments, mice that received compounds SR-N62-55A or SR-N62-55B exhibited significant habituation on day-2 exploring as compared to minimal habituation in vehicle mice ($p=0.0013$). Similar levels of effectiveness were found at the 10 and 20 mg/kg dosages tested. From immunoblotting, the improved behavioral performance correlated with improved synaptic marker levels (29.5% increase in GluA1) in hippocampal samples of the N62-55A-treated mice ($p=0.034$). Improved memory was also found in a Fischer rat model of MCI using passive avoidance testing. Oral PK and brain:plasma work is completed. The next scheduled studies include testing lead molecules in 5xFAD mice to develop a disease-modifying treatment that improves clearance of multiple types of pathogenic proteins and molecular complexes, with the potential to prevent the onset and/or limit the progression of AD proteinopathy.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.12/V21

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

Support: MOST111-2321-B001-010
NSTC112-2321-B001-008
NSTC113-2321-B001-011
NSTC114-2321-B001-007
NSTC115-2321-B001-006

Title: Tau-Induced Nucleotide Metabolic Imbalance Is Associated with ENT1-Dependent Mitochondrial Regulation

Authors: *Y. CHANG[1], C.-P. CHANG[2], Y. CHERN[3];
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Abstract: Abnormal tau protein aggregation is a common pathological feature acrossmultiple neurodegenerative diseases and has been increasingly linked tometabolic dysfunction. Using the SH-SY5Y-Tau human neuroblastoma cell line,we found that tau induction altered purine and pyrimidine metabolism,suggesting a disruption of nucleotide metabolic homeostasis. These findingsraise the possibility that tau-induced metabolic imbalance creates a demand fornucleoside transport to maintain mitochondrial function. Consistent with thishypothesis, ENT1 overexpression enhanced mitochondrial function under tau-expressing conditions. Using mitochondrial isolation, immunofluorescence,proximity ligation assay, and immunoprecipitation, we further found that ENT1localizes to both the mitochondrial outer and inner membranes, suggesting apotential role in mitochondrial nucleoside transport. Together, these findingssuggest that ENT1 may help regulate purine and pyrimidine metabolism andsupport mitochondrial function during tau-associated metabolic stress.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.13/V22

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

Title: Masupirdine (5-HT_6 Receptor Antagonist): Baseline Characteristics from a Phase 3 Study in Alzheimer’s Dementia with Agitation

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Abstract: Alzheimer's Disease (AD) is characterized as a progressive neurodegenerative disorder with manifestations of cognitive and neuropsychiatric symptoms (NPS). Agitation is one of the most prevalent and challenging NPS. There remains a void in the available treatment options for managing agitation in terms of modest efficacy, and safety concerns. Serotonin-6 (5-HT_6) receptors are G-protein-coupled receptors with distinct localization and specific distribution in brain regions associated with mood and behavior regulation. Blocking presynaptic 5-HT_6 receptors reduces the inhibitory control exerted by GABAergic interneurons and enhances monoaminergic neurotransmission involved in behavioral control. Masupirdine, a pure, potent, and orally active 5-HT_6 receptor antagonist in development for the treatment of agitation. Post hoc analyses of a Phase-2 clinical study of Masupirdine in patients with AD (NCT02580305) indicated that the treatment significantly improved agitation/ aggression. Masupirdine is currently being evaluated in a pivotal global Phase-3 double-blind, randomized, placebo-controlled, parallel group, multicenter study evaluating the efficacy, safety, tolerability and pharmacokinetics of Masupirdine for the treatment of agitation in patients with dementia of the Alzheimer's type (NCT05397639; EudraCT: 2021-003405-22). Study will assess effect of Masupirdine at doses of 50 mg and 100 mg as compared to placebo, in approximately 375 patients recruited from the USA and Europe. The primary endpoint is the change in scores on the Cohen-Mansfield Agitation Inventory (CMAI) items that align with the International Psychogeriatric Association (IPA) agitation criteria domains. At approximately 50% enrollment, mean age of the study population was 71.7 years, with females comprising 60.5% of the sample. Geographically, most participants were from North America (74.2%). Majority of the study population were White (92.1%). Regarding clinical characteristics, the mean CMAI total score was 63.6, and the CMAI-IPA score averaged 39.4. The mean Neuropsychiatric Inventory (NPI-12) total score was 38.7, with an agitation/aggression subscale (NPI-12 A/A) mean of 7.4. The Clinical Global Impression-Severity (CGI-S) score averaged 4.6, and the mean Mini-Mental State Examination (MMSE) score was 18.5. Baseline characteristics are consistent with other studies and representative of an AD population with agitation. Currently, over 90% of the study subjects have been enrolled. Results from this Phase-3 study will inform the clinical utility of Masupirdine for the management of agitation in AD.

Disclosures: R. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A.K. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **D. Dogiparti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Mohammed:** A.

Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.14/V23

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

Support: NIH R01 AG066080
NIH R01 AG071656
Alzheimer's Association PTC-17- 439955

Title: Long-term persistence and safety of AAV-NGF gene therapy beyond 15 years in human Alzheimer's disease

Authors: *H. ZIA[1], Y. MAGAÑA[2], D. BARBA[3], B. T. HARRIS[4];
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Abstract: Gene therapy is a rapidly evolving technology that is already approved for several human diseases, including spinal muscular atrophy. Adeno-associated virus (AAV) vectors are the most common vector for clinical gene delivery, but questions have arisen regarding their long-term safety and risk of inflammation. Here we report that expression of nerve growth factor (NGF) persists for 15 years without apparent toxicity or significant immune response after direct brain injection of AAV2-NGF in early Alzheimer's disease (AD).

In 2001, we initiated the first clinical program of gene therapy in early AD to test the hypothesis that the neurotrophic factor NGF would preserve cholinergic neuron function. Degeneration of cholinergic neurons occurs early in AD and contributes to cognitive decline. Preclinical studies found that NGF prevents cholinergic neuron death and stabilizes cholinergic projections to the cortex and hippocampus. Over the next 15 years, a total of 33 early AD patients received NGF gene delivery by direct injection of AAV2-NGF targeting the nucleus basalis of Meynert. In Phase 2 of the clinical trial, AAV2-NGF did not slow cognitive decline compared to sham surgery controls, but most injections (>90%) missed their target or failed to spread to cholinergic neurons as determined by pathological analysis of 10 cases.

We examined these 10 brains to assess the safety of AAV2-NGF injection, given recent reports that AAV2 may cause inflammation and cellular toxicity. We found no evidence of cellular toxicity by immunolabeling for markers of T and B lymphocytes, microglia, and astrocytes. While microglia were present in regions of NGF expression, they were not associated with neuronal loss. Moreover, NGF gene expression remained detectable for at least 15 years after treatment, the longest time point received to date.

We conclude that AAV2 supports safe and long-lasting gene expression for at least 15 years in the degenerating human brain.

Disclosures: H. Zia: None. **Y. Magaña:** None. **D. Barba:** None. **B.T. Harris:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.15/Web Only

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

Title: Comparing Generative AI Models for Alzheimer's Disease Drug Repurposing with Clinical Validation

Authors: *S. REN;
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Abstract: Introduction: Alzheimer's Disease (AD) is a severe disease with limited therapeutic options, presenting a critical unmet medical need. Drug repurposing offers a cost-effective strategy to accelerate therapeutic discovery compared to conventional drug discovery methods. While generative artificial intelligence (GAI) has emerged as a tool for identifying drug candidates, the comparative efficacy of different model architectures remains understudied. This study evaluated and compared three GAI models for their ability to generate viable AD drug-repurposing candidates, contrasting two non-thinking models (GPT-5.5 and Gemini 3 Flash) with one thinking model (Claude Sonnet).
Methods: We iteratively prompted three GAI models to identify the 20 most promising drugs for AD repurposing. To validate these selections against real-world evidence, we utilized electronic health record (EHR) data from the All of Us Research Program. Cox proportional hazards regression analysis was employed to evaluate the longitudinal association between candidate drug exposure and AD incidence among individuals aged 65 and older, adjusting for key demographic comorbidities.
Results: The GAI models generated distinct lists of drugs with varying degrees of overlap (Table 1). A total of 95 drugs were identified for AD repurposing. While limited by sample size and confounding factors, the real-world EHR validation was able to confirm some high-frequency recommendations, including specific anti-diabetic and metabolic agents. Among the most commonly recommended drugs for repurposing were Metformin, Pioglitazone, and Semaglutide.
Conclusion: This study establishes a robust pipeline integrating GAI-driven target discovery with real-world clinical validation. Our findings demonstrate that GAI models can effectively prioritize viable drug repurposing candidates for AD, with performance varying by model architecture. In addition, the drugs identified are great candidates for future research and may inform treatment options for managing comorbidities in patients at high risk for AD.

Table 1

Most frequently identified drug-repurposing candidates for AD by GAI model

Drug	GPT-5.5 Frequency	Gemini 3 Flash Frequency	Claude Sonnet 4.6 Frequency	Total Frequency
Metformin	10	10	7	27
Pioglitazone	10	10	6	26
Semaglutide	10	8	7	25
Liraglutide	9	9	4	22
Lithium	10	2	7	19
Losartan	10	1	7	18
Bumetanide	1	9	7	17
Minocycline	9	0	7	16
Sildenafil	5	10	1	16
Simvastatin	7	1	7	15

Disclosures: S. Ren: None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.16/V24

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

Support: Regions Hospital Foundation
Sexton Family Foundation

Title: Intranasal Delivery of Deferoxamine Promotes Lysosomal Uptake in Rat Brain In Vivo

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Paul, MN; [3]Ctr. for Memory and Aging, HealthPartners Inst., SAINT PAUL, MN; [4]Neurosci. Res., HealthPartners Inst., Vadnais Heights, MN; [5]Neurosci., HealthPartners, St Paul, MN

Abstract: Deferoxamine (DFO), a natural chelator with a high affinity for iron, has been shown to be neuroprotective in several neurodegenerative diseases and neurological insult. Because it is beneficial across several conditions there is likely an underlying non-disease specific multifunctional mechanism of neuroprotection. DFO is a well-established inhibitor of ferroptosis, an iron-dependent form of regulated cell death, which is likely a factor. Lysosomes act as an important part of this process because of their role in storage and regulation of iron. *In vitro* studies have shown that DFO enters cells via endocytosis and subsequently enters lysosomes where it can play a role in iron storage and release. However, this has not been demonstrated directly *in vivo* in neuronal tissue. In this study a single dose of intranasally administered DFO (IN DFO; 6 mg) was given to rats (n=6/group) and brain tissue subsequently analyzed to determine whether DFO entered lysosomes and effected iron storage within these lysosomes at 10, 30, 60, and 240 min after delivery. This study utilized a commercially available kit to isolate lysosomes from post-mortem brain tissue, liquid chromatography electrospray ionization mass spec/mass spectrometry (LC-ESI-MS/MS) to quantify DFO and inductively coupled plasma mass spectrometry (ICP-MS) to quantify iron. The data demonstrated that DFO did enter lysosomes in brain tissue, though it was near the limit of detection and was only detectable in the samples 10 minutes after delivery. Total iron was also quantifiable in the samples and there did appear to be weak correlative increase in iron for samples at 10, 30, and 60 min after delivery ($p < 0.1$). Although the quantification of DFO was close to the limit of detection, to our knowledge, this is the first direct evidence of the uptake of DFO in neuronal lysosomes *in vivo*.

Disclosures: J.M. Fine: None. **S.P. Swanson:** None. **K.A. Faltesek:** None. **W.H. Frey:** None. **L.R. Hanson:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.17/V25

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

Title: Investigating TDP-43 Loss of Function and Nucleocytoplasmic Transport Defects in Sporadic Alzheimer's Disease Using Patient iPSC-derived Cortical Neurons

Authors: *P. CHAKRABORTY[1], S. AKERMAN[2], M. DU[3], A. N. COYNE[4], J. D. ROTHSTEIN[5];
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Abstract: TAR DNA-binding protein 43 (TDP-43) pathology is observed in more than 30-70% of Alzheimer's disease (AD) cases and is associated with fast-paced cognitive decline, hippocampal damage, and memory loss. While TDP-43 dysfunction has been well characterized in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), its role in sporadic Alzheimer's disease (sAD), particularly through loss-of-function (LOF) mechanisms, remains poorly understood. We hypothesized that nuclear TDP-43 loss of function (LOF) occurs in neurons derived from sporadic Alzheimer's disease (sAD) patient iPSCs and contributes to neurodegeneration through the disruption of nucleocytoplasmic transport (NCT), aberrant RNA processing, and proteostatic stress. To investigate this, induced pluripotent stem cell (iPSC)-derived cortical neurons generated from sAD patients and age-matched healthy controls were differentiated to mature neuronal stages to examine neuronal identity using immunocytochemistry. Markers of cortical specificity, neuronal maturation, morphology, and synaptic maturation were used. TDP-43 LOF was evaluated using quantitative PCR analysis of established LOF-associated transcripts, including STMN2 and truncated STMN2 (tr-STMN2), and additional neuronal targets involved in RNA dysregulation. Preliminary observations indicate emerging variability in TDP-43-associated transcript profiles, including differential expression of STMN2 and tr-STMN2 in sAD-derived cortical neurons relative to controls. In parallel, immunocytochemical analysis revealed changes in TDP-43 and Lamin B1 localisation, accompanied by differences in nuclear morphology and protein distribution patterns. Postmortem brain tissue from the iPSC donors is also being investigated to elucidate whether these phenotypes are conserved in human disease. Together with experiments determining NCT and subsequent rescue experiments, this work will clarify whether TDP-43 LOF and NCT dysfunction represent convergent mechanisms contributing to neuronal degeneration in sporadic AD and may identify novel therapeutic targets for disease intervention.

Disclosures: P. Chakraborty: None. **S. Akerman:** None. **M. Du:** None. **A.N. Coyne:** None. **J.D. Rothstein:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.18/V26

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

Support: NIH Grant 5R01 AG072643
NIH Grant 5U19 AG065169

Title: Lithium engages an NPTX2-centered synaptic resilience program associated with cognitive maintenance

Authors: *M. XIAO[1], K. KIM[2], K. LISSIT[1], Y. HUANG[1], Y. LAO[1], M. FAN[1], L. L. TALIB[4], M. HUENTELMAN[5], C. A. BARNES[6], O. FORLENZA[4], J. XU[2], C.-H. NA[2], P. F. WORLEY[3]; [2]Neurol., [3]Dept Neurosci/Neurol, [1]JHMI, Baltimore, MD; [4]Psychiatry Inst. HCFMUSP, São

Paulo, Brazil; [5]Neurogenomics, TGen, Phoenix, AZ; [6]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ

Abstract: Lithium exposure has been associated with reduced risk of dementia and slower cognitive decline, but the molecular pathways underlying its neuroprotective effects remain unclear. We analyzed archived plasma and cerebrospinal fluid (CSF) samples from a randomized, placebo-controlled trial of low-dose lithium treatment in individuals with amnestic mild cognitive impairment (aMCI) to identify biomarkers associated with lithium exposure and cognitive maintenance.Among CSF proteins measured by ELISA, NULISA, and targeted mass spectrometry, neuronal pentraxin 2 (NPTX2) emerged as a unique candidate linking lithium exposure to clinical outcome: plasma lithium concentrations scale with CSF NPTX2 change, and CSF NPTX2 change tracks cognitive trajectories as measured by Clinical Dementia Rating-Sum of Boxes scores. Multiplex NULISA and PRM-MS profiling further shows that cognitive maintenance associates with an NPTX2 circuit-refinement signature including NPTX1, NPTXR, the parvalbumin-interneuron AMPA receptor subunit GluA4, and proteins involved in microglial cytokine signaling.To investigate underlying mechanisms, we examined lithium regulation of NPTX2 in experimental models. Lithium robustly increased NPTX2 mRNA and protein expression in primary hippocampal neurons but not cortical neurons. Similar hippocampus-selective induction was observed in mice following chronic lithium administration, with elevated NPTX2 expression in hippocampal CA3 and hilar regions. Lithium also increased NPTX2 expression in human iPSC-derived hippocampal organoids, whereas no induction was observed in iPSC-derived cortical neurons. NPTX2 induction was not reproduced by selective GSK3 inhibitors and was not blocked by acute BDNF scavenging, indicating a pathway distinct from canonical lithium targets.Together, these findings identify NPTX2 as a lithium-responsive biomarker and nominate an NPTX2-centered synaptic resilience program as a potential mechanism supporting cognitive maintenance.

Disclosures: M. Xiao: None. **K. Kim:** None. **K. Lissit:** None. **Y. Huang:** None. **Y. Lao:** None. **M. Fan:** None. **L.L. Talib:** None. **M. Huentelman:** None. **C.A. Barnes:** None. **O. Forlenza:** None. **J. Xu:** None. **C. Na:** None. **P.F. Worley:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.19/V27

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

Support: 5R01NS034239-28
University of Nebraska Foundation

Title: Improved preclinical Outcomes by Combinatorial Treg stimulating agent and Anti-Aβ mAb Therapy

Authors: *R. KADRY[1,2], E. FOSTER[2], S. BHATTARAI[2], S. QASIM[2], Y. LU[2], R. MOSLEY[2], P. YEAPURI[2], H. E. GENDELMAN[2];
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia worldwide. The accumulation of misfolded, neurotoxic amyloid-beta (Aß) proteins in AD drives cognitive decline and neurodegeneration. The FDA approved anti-Aß monoclonal antibodies (mAbs) show less than encouraging clinical outcomes. Adverse events are linked to amyloid related imaging abnormalities associated with edema and microhemorrhages (ARIA-E/H). These likely arise from anti-Aß mAbs mediated microglial inflammatory responses. This has led to market withdrawal of one approved anti-Aß mAb, Aducanumab.There is an urgent need to develop Aß-targeting immunotherapies that enhance amyloid clearance while minimizing neuroinflammatory responses. We posit that administering of regulatory T-cell (Treg) induction by low dose of interleukin-2 (IL-2) followed by anti-Aß mAbs, can both control microglial activation and produce a homeostatic neuroenvironment. This will improve amyloid clearance and cognitive outcomes. To this end, we developed novel oligomeric anti-Aß mAb (2CD3M) that preferentially binds only to neurotoxic Aß isoforms. The binding profile was comparable to Lecanemab. This was affirmed by surface plasmon resonance (SPR) and immunoprecipitation (IP) assays. To validate therapeutic efficacy, we performed short- (60 days) and long- term (seven month) studies, with 2CD3M and a murine Lecanemab (mAb158). The APP/PS1 transgenic mice were treated with mAb and IL-2 combinatorial, and mAb or IL-2 monotherapy. Combination treatment improved cognition recorded by radial arm water maze tests and reduced amyloid burden. Immunofluorescence results revealed that mAb in combination with IL-2 reduced microgliosis and promoted significant microglia cell recruitment around large Aß plaques. The combination of 2CD3M Aß mAb with low dose IL-2 enhanced amyloid clearance, mitigated microgliosis, neuroinflammation and improved behavioral outcomes when compared to mAb or low dose IL-2 alone. This offers a clinically translatable approach to enhance mAb therapies for AD and supports the further development of this novel translational immunotherapy.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.20/V28

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

Title: Polyphenol-loaded Nanocapsules as a Potential Multi-target Intervention for Alzheimer’s Disease

Authors: *G. FUHR[1], M. ORSATTO HAAS[2], M. FACCIN HUTH[2], K. ADAM MELLO[2], J. CAPP ZILLES[2], R. VIDOR CONTRI[2], A. ZIMMER[2];
[1]Grad. Program in Pharmaceut. Sci., Federal Univ. of Rio Grande do Sul, Novo Hamburgo, Brazil; [2]Federal Univ. of Rio Grande do Sul, Porto Alegre, Brazil

Abstract: Alzheimer's disease (AD) pathology involves neuroinflammation, oxidative stress, and cholinergic deficits. While polyphenols like luteolin (LUT) and curcumin (CUR) possess pleiotropic neuroprotective properties, their clinical translation is hindered by poor bioavailability. Nanoparticle delivery systems represent a promising approach for efficiently crossing the blood-brain barrier. Here, we investigated the multi-target efficacy of polyphenol-loaded nanocapsules (NCs) containing CUR and LUT across in vitro and in vivo models. To evaluate cellular recovery, C6 astroglial, HT22 neuronal, and BV2 microglial cells were exposed to oxidative (H_2O_2) or inflammatory (LPS) insults, with viability assessed via MTT assay (≥3 independent experiments). To evaluate cholinergic modulation, acute anterograde amnesia was induced via scopolamine (SCO) (2 mg/kg) in 2-month-old male and female CF-1 mice (n=4-6/group). Cognitive acquisition was evaluated using the Novel Object Recognition (NOR) test. In vitro, NCs robustly restored cell viability following H_2O_2 toxicity in C6 and HT22 cells, and reversed LPS-induced cytotoxicity in BV2 cells (One-way ANOVA with Dunnett's; full statistics detailed graphically) (Figure 1, A-C). In vivo, SCO-treated mice exhibited severe amnesia (Discrimination Index [DI]: 0.14 ± 0.19; Recognition Index [RI]: 0.57 ± 0.09). Conversely, pre-insult administration of polyphenol nanocapsules significantly prevented amnesic deficits, enhancing both DI (0.71 ± 0.05) and RI (0.85 ± 0.02) compared to SCO-treated ($p<0.0001$; One-way ANOVA with Tukey's post-hoc) (Figure 1, D-E). These findings demonstrate that nanocapsule delivery of curcumin and luteolin actively reverses neural cytotoxicity while providing potent in vivo protection against cholinergic amnesia, highlighting a highly translational multi-target nanotherapeutic approach for AD.

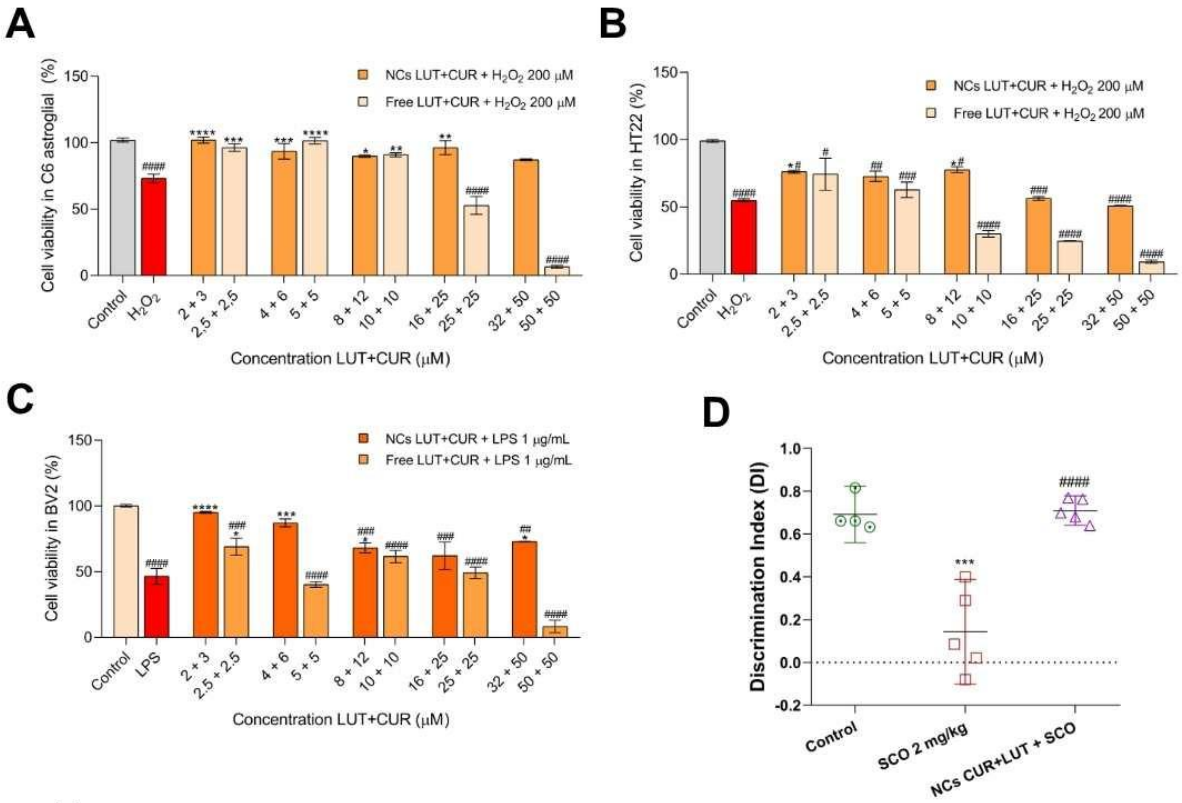


Figure 1. Neuroprotective effect and prevention of cognitive deficits promoted by curcumin- and luteolin-loaded nanocapsules (NCs) in *in vitro* and *in vivo* models. (A-C) Cell viability assays illustrating neuroprotective action against oxidative and inflammatory insults. Across all scenarios, treatment with the NCs demonstrated superior efficacy in restoring cell viability compared to the same compounds administered in free form. (A) C6 astroglial cell line subjected to H_2O_2-induced (200 μM) oxidative stress. (B) HT22 neuronal cell line exposed to H_2O_2 (200 μM). (C) BV2 microglial cell line subjected to lipopolysaccharide (LPS)-induced (1 μg/mL) inflammation.

(D-E) Evaluation of recognition memory in the in vivo model of scopolamine (SCO)-induced (2 mg/kg) amnesia using the Novel Object Recognition (NOR) test. (D) Discrimination Index (DI) demonstrating that the SCO-treated group exhibited a significant reduction in discriminatory capacity compared to the control group. Treatment with NCs prevented this deficit, maintaining the DI at levels that did not differ statistically from the control. (E) Recognition Index (RI) corroborating memory preservation in the NC-treated group, whereas the SCO group exhibited significant impairment in exploring the novel object.

Data are expressed as mean ± SD for *in vitro* and *in vivo*. For *in vitro:* Symbols indicate significant statistical difference (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ vs. Insult; # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$; #### $p < 0.0001$ vs. Control) determined by One-way ANOVA followed by Dunnett's post-hoc test. For *in vivo*: Symbols indicate significant statistical difference (*** $p < 0.001$ vs. Control; #### $p < 0.0001$ vs. SCO) determined by One-way ANOVA followed by Tukey's post-hoc test.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.21/W1

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

Support: NIH R01AG 55549
UG3/UH3 NS 113776

Title: Evaluation of Safety and Efficacy of a Novel Mitochondrial Complex I Inhibitor C273 in 5xFAD Mice

Authors: *M. OSTROOT[1], S. TRUSHIN[2], T. KOVALENKO[1], J. NESBITT[1], E. TRUSHINA[3]; [2]Neurol., [3]Dept. of Neurol., [1]Mayo Clin., Rochester, MN

Abstract: Mitochondrial dysfunction is an early and central feature of Alzheimer's disease (AD). We identified mitochondrial complex I (mtCI) as a druggable target and demonstrated that weak, reversible inhibition of mtCI activates AMPK, leading to neuroprotection in multiple *in vitro* and *in vivo* experimental models of AD. These findings suggest that modulating mtCI activity with small molecules may provide therapeutic benefits without toxic side effects. Using rational design and extensive structure-activity relationship studies, we developed a novel weak mtCI inhibitor C273, with high selectivity, specificity, and improved drug-like properties. Pharmacokinetic and pharmacodynamic studies established bioavailability and the blood-brain barrier (BBB) penetration. Safety was evaluated using the CEREP 44 safety panel; *in vivo* safety was established by chronic administration of C273 to C57BL/6 mice. *In vivo* efficacy was assessed in the 5xFAD mice. C273 readily crossed the BBB and activated AMPK in the mouse brain, triggering an adaptive neuroprotective stress response. The compound demonstrated excellent bioavailability and a clean safety profile in the CEREP 44 panel. Daily administration of C273 (20, 50, or 80 mg/kg/day) to C57BL/6 mice for one month produced no detectable adverse effects or toxicity in the heart or liver. Chronic treatment of 5xFAD mice with C273 (20 mg/kg/day, administered in drinking water *ad lib*) for one month improved nest construction, an ethologically relevant measure of goal-directed behavior and functional capacity that depends on intact cortical, hippocampal, and metabolic processes. This was reversed following a withdrawal of C273 treatment, indicating a treatment-dependent effect. These *in vivo* studies demonstrate that C273 is a safe, brain-penetrant, weak mitochondrial complex I inhibitor that provides neuroprotection in the 5xFAD mouse model of AD. The favorable safety profile, sustained efficacy, and excellent ADMET properties of C273 support its advancement as a strong preclinical candidate for AD therapy. Importantly, these findings highlight that *partial and reversible inhibition of mtCI* can engage an adaptive mitochondrial stress response, preserving neuronal function without inducing toxicity. Collectively, this work establishes weak mtCI inhibition as a viable and disease-modifying therapeutic strategy for Alzheimer's disease, supporting further translational development of C273.

Disclosures: M. Ostroot: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **S. Trushin:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research. **T. Kovalenko:** None. **J. nesbitt:** None. **E. Trushina:** E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named inventor on one or more patent applications owned by Mayo Foundation for Medical Education and Research.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.22/W2

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

Support: NIH Grant R01AG070873
New Jersey Commission on Brain Injury Research Grant CBIR23IRG008

Title: Inhibition Of Mitochondrial Cyclic Nucleotide Signaling Improves Mitochondrial Dynamics And Memory Deficits In Alzheimer’s Disease

Authors: *B. DOU[1], F. XU[2], X. ZHU[4], Y. XU[3];
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Abstract: Mitochondrial cyclic nucleotide signaling regulates mitochondrial respiration, thereby influencing mitochondrial function. As the primary enzyme that hydrolyzes cyclic nucleotides, phosphodiesterase 2 (PDE2A) plays a significant role in regulating mitochondrial cAMP and cGMP levels; however, the precise mechanism remains unclear. This study investigated the role of aberrant PDE2A signaling in driving mitochondrial dysfunction and cognitive deficits in a mouse model of Alzheimer’s disease (AD), using both pharmacological inhibition and genetic deletion of PDE2A. We found that elevated PDE2A expression in the brains of AD patients and APP/PS1 mice was associated with progressive age-dependent reductions in cAMP and cGMP levels in both the cytosol and mitochondria. Treatment of hippocampal neuronal cells (HT22) with the PDE2A inhibitor Bay 60-7550 (Bay) protected against amyloid-β42 (Aβ42)-induced neuronal death. Genetic deletion of PDE2A significantly ameliorated mitochondrial dynamics dysfunction by restoring mitochondrial cyclic nucleotide pools, thereby improving cognitive performance and reducing AD-related pathological features in APP/PS1 mice. Conversely, re-expression of mitochondrial PDE2A2 in PDE2A-deficient cells restored mitochondrial dysfunction by inhibiting PKA/PKG-mediated phosphorylation of the mitochondrial fission protein dynamin-related protein 1 (DRP1) at Ser637 and enhancing its mitochondrial translocation. Collectively, these findings identify mitochondrial PDE2A as a critical regulator of the cyclic nucleotide-DRP1 signaling axis and establish a mechanistic link between PDE2A dysregulation and AD-associated pathological mitochondrial remodeling.

Disclosures: B. Dou: None. **F. Xu:** None. **X. Zhu:** None. **Y. Xu:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.23/Web Only

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

Title: Low-dose methylprednisolone treatment for five weeks improves cognitive function and hippocampal postsynaptic integrity in TgF344-AD rats by targeting Abeta-mediated inhibition of KIF11/Eg5 activity

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Abstract: Progressive amyloid-beta (Abeta) toxicity contributes to synaptic dysfunction and cognitive decline in Alzheimer's disease (AD). We previously showed that Abeta inhibits the kinesin motor protein KIF11/Eg5, impairing intracellular transport and neuronal function. Using a KIF11/Eg5 ATPase-based screening assay, we identified methylprednisolone (MP) as a candidate compound that reduces Abeta-mediated KIF11/Eg5 inhibition in vitro. We evaluated MP efficacy in male and female TgF344-AD rats treated with MP (10 mg/kg) or saline twice weekly for five weeks. Cognitive performance was assessed by RAWM and contextual fear conditioning (CFC). MP-treated male TgF344-AD rats showed significant improvement in RAWM performance, while both sexes exhibited a trend toward improved CFC performance. Overall, behavioral analyses supported a beneficial cognitive effect with MP treatment. To examine pathological changes, hippocampal regions from sagittal brain sections were analyzed for PSD95 as a marker of postsynaptic neuronal integrity, and for GFAP as a marker of astrocytic activation. Preliminary analyses revealed increased hippocampal PSD95 density in female MP-treated TgF344-AD rats, suggesting preservation and/or restoration of postsynaptic structure. Also, female TgF344-AD rats exhibited greater PSD95 density than male TgF344-AD rats in our cohort, a finding consistent with reported sex-dependent differences in hippocampal synaptic organization. In contrast, hippocampal GFAP expression was not altered significantly by MP treatment. Together, these findings suggest that MP treatment may improve cognitive function through preservation of synaptic integrity downstream of Abeta-mediated inhibition of KIF11/Eg5 ATPase activity rather than through modulation of astrocytic activation. These findings support MP as a potential therapeutic candidate that targets Abeta-mediated inhibition of KIF11/Eg5 ATPase activity in AD.

Disclosures: A. Wang: None. **P. Grissom:** None. **C. Heitmann:** None. **H.J. Chial:** None. **H. Potter:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.24/W3

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

Support: NSFC Grant 82361138569
NSFC Grant 81961138015
NSFC Grant 82372012

Title: Photo-sleep therapy boosts brain drainage and clearance

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Abstract: Non-invasive photobiomodulation has been recognized as a safe and efficient approach for mitigating neuropathology in neurodegenerative disorders or brain injury, primarily through the improvement of brain drainage function. Nevertheless, conventional photobiomodulation applied during wakefulness (awake photobiomodulation) frequently yields suboptimal therapeutic outcomes, owing to strong scattering by the skull and the presence of advanced disease pathology. Interestingly, non-rapid eye movement (NREM) sleep is known to promote brain drainage, mitochondrial repair, and phagocytic activity of immune cells, thereby offering a potential amplification window for photobiomodulation-based interventions. In this work, we introduce a closed-loop photo-sleep modulation strategy that delivers photobiomodulation precisely during NREM sleep. Relative to awake photobiomodulation, photo-sleep therapy produced superior enhancement of brain drainage dynamics and greater reduction of pathological burden in mice (such as AD, TBI) accompanied by improved cognitive performance, diminished neuroinflammation, and strengthened neuroprotection. At the mechanistic level, photo-sleep therapy upregulated matrix metalloproteinase (MMP) activity in parenchymal border macrophages (PBMs) to a greater extent than awake photobiomodulation, thus establishing a more permissive perivascular microenvironment for arterial pulsation and facilitating more efficient brain drainage. Pharmacological activation of PBMs using colony-stimulating factor elevated MMP activity and boosted drainage efficiency, whereas depletion of PBMs with clodronate-encapsulated liposomes eliminated the advantage of photo-sleep therapy over awake photobiomodulation, underscoring the essential role of PBMs in mediating the therapeutic effects of photo-sleep therapy. Taken together, these findings present a potent, patient-friendly, and easily implementable modality for non-invasive treatment of brain diseases, holding considerable promise for rapid clinical adoption.

Disclosures: H. Lin: None. **S. Liu:** None. **J. Li:** None. **Q. Yang:** None. **W. Yang:** None. **Z. Wang:** None. **D. Zhu:** None. **T. Yu:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.25/W4

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

Support: Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project 2022ZD0211605
National Natural Science Foundation of China U24A20681
National Natural Science Foundation of China 82471210
Beijing Hospitals Authority's Ascent Plan DFL20240806

Title: Real-world neuropsychiatric and cognitive responses to lecanemab and donanemab from subjective cognitive decline to dementia in Alzheimer's disease in China

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Abstract: Introduction: Lecanemab and donanemab target β-amyloid in Alzheimer's disease (AD). Evidence remains limited in patients with subjective cognitive decline (SCD), those with Mini-Mental State Examination (MMSE) scores <18, apolipoprotein E (APOE) ε4 homozygotes, individuals at extremes of age, and atypical Aβ-positive phenotypes such as posterior cortical atrophy (PCA). The effects of the two agents on neuropsychiatric symptoms remain unclear. **Methods:** Aβ-PET-positive individuals receiving lecanemab (n=355) or donanemab (n=132) were recruited, of whom 175 had available 6-month follow-up data for cognitive, neuropsychiatric, biomarker, Aβ-PET, and safety assessments. **Results:** At 6 months, neuropsychiatric symptoms showed overall improvement. In the lecanemab group, Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) scores were significantly reduced from baseline (HAMD: −1.49 points, $P = 0.017$; HAMA: −3.26 points, $P = 0.036$). In the donanemab group, HAMD and HAMA scores also decreased, although the changes did not reach statistical significance (HAMD: −1.32 points, $P = 0.064$; HAMA: −1.50 points, $P = 0.091$). Cognitive measures showed trends toward improvement in both treatment groups, including MMSE scores (lecanemab: +0.04 points, $P = 0.105$; donanemab: +0.62 points, $P = 0.054$) and Montreal Cognitive Assessment (MoCA) scores (lecanemab: +0.27 points, $P = 0.248$; donanemab: +0.37 points, $P = 0.246$). When stabilization was defined as no decline or improvement from baseline, more than 50% of patients with SCD or moderate-to-severe AD dementia showed stabilization in MMSE or MoCA scores, and neuropsychiatric improvement was also observed in these underrepresented groups. Similar patterns were seen across APOE ε4 genotypes and age categories. Plasma P-tau217 decreased significantly from baseline in both groups, with numerically lower 6-month levels after donanemab than lecanemab but no significant between-group difference (P=0.608). Aβ-PET suggested greater global and regional amyloid-burden reductions after donanemab, particularly in posterior cingulate, precuneus, inferior parietal, and lateral temporal regions. Amyloid-related imaging abnormalities (ARIA) and infusion-related reactions (IRRs) were monitored during follow-up, with no unexpected safety signals observed. **Conclusion:** Over 6 months, lecanemab and donanemab were associated with short-term improvement in AD-related neuropsychiatric symptoms and mild improvement

or stabilization in cognitive scores among Aβ-PET-positive individuals from SCD to moderate-to-severe AD dementia, including atypical clinical phenotypes.

Disclosures: Y. Xu: None. **S. Huang:** None. **X. Cheng:** None. **L. Jia:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.26/W5

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

Title: Gamma-Band EEG Response States as Predictors of Outcome of 40-Hz MultimodalSensory Stimulation in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is associated with progressive cognitive and functional decline. Gamma-frequency neural activity [30-100Hz] is implicated in cognition and may be modulated non-invasively through rhythmic sensory stimulation. The OVERTURE feasibility study [NCT03556280], a randomized, double-blind sham-controlled trial, demonstrated that daily Spectris™ (Cognito Therapeutics, Cambridge, MA) 40-Hz auditory and visual stimulation reduced the decline in cognitive and functional abilities, as well as brain atrophy in individuals with mild-to-moderate AD. This exploratory analysis of data from the OVERTURE study investigated whether EEG responses to stimulation define neural response states associated with clinical trajectory. EEG was recorded at baseline, week 12, and week 24 using 32- or 64-channel ANT-Neuro eego systems. Data were filtered, re-referenced to common average, cleaned using ICA-based artifact removal, and segmented into 2 second epochs. For each epoch, Welch power spectral density was used to extract absolute and relative low-gamma [30-55Hz] and high-gamma [55-80Hz] power. Hierarchical clustering, guided by silhouette analysis, identified EEG response states across participants and time points.
Clustering identified three gamma-band response states. Cluster 1 showed low gamma activity, Cluster 2 showed broadly elevated gamma activity, and Cluster 3 showed a dissociated gamma profile, with suppressed low-gamma and elevated high-gamma power. Cluster 3 was the smallest and most transient response state. Participants were classified as Cluster 3 responders if they exhibited at least one stimulation epoch classified as Cluster 3 during treatment. Only active stimulation showed C3→C2 transitions through week 24. Clinical analyses were stratified by treatment arm and baseline CDR-SB severity, with higher impairment defined as baseline CDR-SB ≥4.5. In active treatment [N=46], Cluster 3 responders with higher baseline impairment

showed CDR-SB stabilization compared with non-responders over 24 weeks (p=0.0021). These findings suggest that gamma-band EEG response states during 40-Hz sensory stimulation may serve as candidate electrophysiological markers of treatment responsiveness in AD.

Disclosures: D. Perez: None. **T. Macedo e Cordeiro:** None. **D.B. Neidre:** None. **A. Teixeira:** None. **G.A. de Erausquin:** 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.; COGNITO Therapeutics Inc..

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.27/W6

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

Support: 1 R01AG081258-01A1
1RF1NS132291-01
1R01AG081874-01
22TPA97025
24POST1196128
25POST1373581

Title: Photobiomodulation improves cerebral blood flow and behavior impairments in a mouse model of Alzheimer's Disease

Authors: *P. RODRIGUEZ, Jr[1], C. T. CITADIN[2], M. UDO[4], B. BRITO NANNI[1], D. J. SMITH[2], J. ZACCARELLI MAGALHÃES[3], J. LANGMAN[2], H. LIN[2];
[2]Neurol., [3]Dept. of Neurol., [1]UTHealth Houston, Houston, TX; [4]Neurol., Univ. of Texas Hlth. at Houston, Houston, TX

Abstract: Background: Alzheimer’s disease (AD) the most common form of dementia globally. Women are more prone to develop AD than men. Emerging evidence has indicated chronic cerebral hypoperfusion, blood brain barrier (BBB) leakage, and impaired brain metabolism as an early pathological hallmark of AD. As a result, the brain suffers from aggressive inflammatory state, driving reactive gliosis, and ultimately loss of neurons. Thus, improving cerebral perfusion may offer a novel therapeutic avenue to prevent, or stop disease progression. Photobiomodulation (PBM) is a non-invasive method that uses near infrared light that has been shown to penetrate the skull and improve cerebral blood flow, metabolism and inflammation. Additionally, preliminary work from our lab has shown that PBM modulates the expression of protein arginine methyltransferase (PRMT) enzymes which have been linked to impaired cerebral hypoperfusion in AD mice. Thus, our work here aims to characterize PBM as a potential novel therapeutic option to treat AD. **Methods:** Aged (between 8- to 12-month-old) male and

female 3xTg-AD and C57BL/6J mice were exposed to a continuous-wave low-level laser (808 nm, 25 mW/cm^2) placed 35 cm above the animal's scalp to generate an area of 1.5 cm^2, for 2 min/day, 3x/week, for 14 days. After the treatment, we evaluated the animal 1) microvascular perfusion and BBB permeability using in vivo two photon microscopy coupled to whisker stimulation 2) measurement of candidate proteins via western blot 3) Cognitive behavioral abilities using novel object recognition and Y-maze tests. **Results:** Our preliminary results show that PBM rescued hypoperfusion in aged 3xTg-AD mice, as well as decreased BBB leakage. Additionally, we show that PBM restores PRMT expression back to Wildtype levels. Finally, we show that PBM restores long term memory in the Novel Object Recognition test. **Conclusion:** Our preliminary results suggest that PBM for 3 months prevents alterations in PRMT expression levels and cerebral perfusion. Based on our data, we believe the improved PRMT expression and prevention of cerebral perfusion is responsible for supporting long term memory in our AD mice. Together, our data suggests that PBM has potential to be used as an alternative/ adjunctive treatment for AD.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.28/W7

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

Support: NIH Grant RF190106435
NIH Grant AG067016
NIH Grant R01AG052510

Title: Human iPSC Derived Neural System Reveals Variable Neuroprotective Responses to Memantine in Alzheimer's Disease

Authors: C. ZIVKO[1], ***R. SAGAR**[2], W. AHMED[1], A. XYDIA[1], F. FARINELLI[3], I. OSTLUND[4], D. DAS[4], B. MAHER[5], C. LYKETSOS[6], V. MAHAIRAKI[1];
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Abstract: INTRODUCTION: Alzheimer's disease is a heterogeneous neurodegenerative condition characterized by progressive cognitive and functional impairment. Memantine, an N-methyl-D-aspartate receptor antagonist, is used in moderate-to-advanced AD, but its neuroprotective benefit varies across individuals. Human iPSC-derived neurons provide a personalized platform to predict memantine's effectiveness against calcium dysregulation and

oxidative stress.
METHODS: We generated iPSC-derived glutamatergic neurons from 19 individuals (12 AD and 7 healthy). Assays for calcium influx and oxidative stress were developed and optimized for neurons. Memantine was tested under different treatment conditions. Neurons were exposed to glutamate/glycine to induce calcium influx and menadione to generate oxidative stress. Memantine treatment was applied either acutely (1 hour) or as a 24-hour pre-treatment to evaluate its neuroprotective effects.
RESULTS: The mean ages of AD patients and healthy controls were 74.5±10.4 and 82.3±4.3 years, respectively; 47% of subjects were female. These iPSCs were successfully differentiated into functional neurons, exhibiting comparable electrophysiological properties between AD and healthy lines. Calcium influx assays revealed heterogeneous responses between AD and healthy neurons, with AD neurons generally exhibiting higher baseline fluorescence. Memantine treatment for 24 hours significantly reduced calcium influx, with an average reduction of -9.85% and a range of -0.39% to -39%. Similarly, ROS assays showed that menadione-induced oxidative stress was attenuated by 24-hour memantine pre-treatment, with a mean reduction of -26.05% and a range of -4.23% to -72.21%. The observed variability indicates differential susceptibility to excitotoxicity reduction and or oxidative stress mitigation across individuals.
CONCLUSION: This study shows a robust in vitro platform for testing memantine efficacy, using iPSC-derived neurons to model calcium dysregulation and oxidative stress in AD. The observed heterogeneity in response underscores the need for personalized approaches in AD treatment and the potential of iPSC-based platforms in precision medicine.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.29/W8

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

Support: Kent State University Graduate Student Senate Research Award

Title: Scaffold-Guided Expansion of Date Palm-Derived Chemical Space Reveals Candidate CDK5/p25 Modulators

Authors: *M. K. AJENIKOKO, M. OSO, R. CLEMENTS;
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Abstract: Aberrant activation of cyclin-dependent kinase 5 (CDK5) by its pathological activator p25 contributes to neurodegenerative disease through dysregulated neuronal signaling, neuroinflammation, and neuronal loss. We previously identified eighteen phytochemicals from

date palm extracts using GC-MS analysis and demonstrated their potential interactions with the CDK5/p25 complex through molecular docking. To expand the therapeutic potential of these natural-product scaffolds, structurally related compounds were identified from public chemical databases and assembled into a focused library of 230 molecules. Virtual screening against the CDK5/p25 complex identified multiple compounds with favorable predicted binding affinities. Top-ranked candidates were subsequently evaluated using molecular dynamics simulations and MM-PBSA binding free-energy analyses, enabling prioritization of promising scaffold families for further development. These findings demonstrate the utility of scaffold-guided exploration of chemical space for identifying and prioritizing candidate CDK5/p25 modulators. As an initial step toward biological validation, isoamyl benzoate, one of the original GC-MS-derived phytochemical scaffolds, was evaluated in LPS-stimulated BV2 microglial cells. Preliminary Nile Red fluorescence imaging demonstrated reduced lipid droplet accumulation relative to inflammatory controls, suggesting modulation of microglial inflammatory responses. Together, these findings establish a scaffold-based drug discovery framework that integrates natural-product-derived chemical space expansion, computational lead prioritization, and early cellular phenotyping to support the development of novel CDK5/p25-targeted therapeutics for neurodegenerative disease.

Disclosures: M.K. Ajenikoko: None. **M. Oso:** None. **R. Clements:** None.

Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.30/W9

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

Support: National Institute of Aging Grant 1R15AG091199

Title: Effects of chronic GLP-1/GIP and GLP-1/GIP/glucagon agonist treatments on high-fat diet fed 3xTg-AD mice

Authors: *R. C. SPETH[1], A. STANISAVLJEVIC[2], N. NOTO[3], K. MARTIN[4], D. KUNI[5], V. PULIDO-CORREA[6], A. ARIAS[7], G. SURESH[8], I. PATEL[5], M. PATEL[8], L. MARCANO RAMOS[10], M. S. PARMAR[9], L. S. ROBISON[8];
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Abstract: The success of GLP-1 receptor agonists and newer multi-agonist incretin drugs for obesity and diabetes has generated significant interest in their neurotherapeutic potential,

particularly because metabolic disease is highly comorbid with, and may contribute to, Alzheimer's disease (AD). To assess this, we investigated the effects of the dual GLP-1/GIP agonist tirzepatide (TIRZEP) and the triple GLP-1/GIP/glucagon agonist retatrutide (RETA) in male and female 3xTg-AD mice. Beginning at 3-4 months of age, mice were fed a high-fat diet (HFD) for 10 weeks, then received subcutaneous injections of PBS vehicle, TIRZEP (20 nmol/kg), or RETA (20 nmol/kg) three times weekly for 3 months while maintained on HFD. Wild-type and 3xTg-AD controls received a low-fat diet and vehicle. Outcomes included body weight, food intake, glucose tolerance, blood pressure, and behavioral testing using open field, elevated plus maze, novel object recognition, object placement, Y-maze, and Barnes maze. Brain, heart, kidney, lung, liver, pancreas, visceral and subcutaneous fat, blood, and feces were collected at euthanasia. As expected, drug treatment significantly altered cardiometabolic outcomes, reducing weight gain, adiposity, and blood pressure while improving glucose tolerance. Several effects were more pronounced in females, potentially in part because HFD produced greater baseline metabolic impairment in 3xTg-AD females than males, including increased weight gain, adiposity, and glucose intolerance. Behaviorally, TIRZEP and RETA tended to normalize deficits in exploratory behavior (open field and Y-maze) and spatial memory (Barnes maze) in 3xTg-AD females, whereas anxiety-like behavior and spatial working memory were less affected. Additional behavioral analyses and cohort expansion are ongoing. These data suggest that multi-agonist incretin therapies may improve metabolic dysfunction and select behavioral outcomes in AD under conditions of diet-induced metabolic stress. If supported by ongoing neuropathological analyses (amyloid-β, tau, neuroinflammation), this work could help establish incretin-based drugs as promising candidates for treating AD patients with obesity, diabetes, or related metabolic comorbidities.

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Poster

PSTR262: Alzheimer's Disease Therapeutic Strategies: Other

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR262.31/W10

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

Support: NIH P51OD011106
NIH R01NS124857
NIH RF1NS138787
UWCCC P30 CA014520

Title: Mapping of estrogen receptors ERα and GPER in the female rhesus brain

Authors: *K. M. WILLIAMS[1,2], K. SANTOS[3], V. BONDARENKO[3], J. M. METZGER[5], M. E. EMBORG[3,2,4];

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Abstract: The female hormone estrogen regulates numerous biological processes through genomic and nongenomic pathways mediated by estrogen receptors (ERs) ERα, ERβ, and GPER. A decline in estrogen during menopause has been linked to increased risk of neurodegenerative disorders, yet hormonal replacement for neuroprotection had produced mixed and controversial results. Interestingly, there is limited data on the intracerebral distribution of ERs in primates. Here, we report the mapping of ERα and GPER in the brains of seven female rhesus macaques aged 1.8 to 21.1 years. All subjects were transcardially perfused with heparinized saline followed by 4% PFA. Their brains were extracted, postfixed in 4% PFA for 24 hr, cryoprotected, cut into 40μm coronal sections, and processed for immunohistochemistry against ERα (SP1 clone [1:100], cat.# MA5-14501, ThermoFisher) and GPER ([1:2000], cat.# PA5-28647, Invitrogen). Nineteen brain regions of interest (ROIs) were evaluated: prefrontal cortex, anterior cingulate cortex, primary motor cortex, entorhinal cortex, caudate, putamen, globus pallidus (interior and exterior), amygdala, hypothalamus (mediolateral and arcuate nucleus), substantia nigra, subthalamic nucleus, hippocampus (CA1, CA3, dentate gyrus, subiculum) and thalamus (MD and VL). The relative number of ER+ cells per ROI was scored using a semiquantitative scale of 0-3, where 0 corresponded to no ER+ cells and 3 represented abundant ER+ cells. Additionally, the intensity of ER-immunoreactivity (-ir) was quantified per region using the H-score [Formula of H-score = (1×% area with staining weak staining cells) + (2×% moderate) + (3× %strong)]. Scorers were blind to animal age and ER immunostaining. ERα-ir and GPER-ir were observed on the membrane and intracellularly (cytoplasm and nucleus) in all ROIs of all subjects, with highest expression present in 3-year-old animals. GPER-ir, compared to ERα-ir, was more intense and homogeneously abundant across all ROIs. Semiquantitative analyses confirmed a 2.5 times higher number of GPER+ cells than ERα+ cells. Analysis of H-scores via ANOVA with Tukey multiple comparison test revealed significantly ($P<0.05$) greater GPER-ir compared to ERα-ir for most ROIs and significant differences in ERα-ir across ROIs. Overall, these results demonstrate the widespread and differential expression of ERα and GPER in the female rhesus monkey brain and provide foundational knowledge for understanding the role of estrogen and receptors in neurodegenerative diseases.

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Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.01/W11

Topic: C.03. Parkinson’s Disease

Title: Activating Nrf2 pathway and targeting alpha-synuclein clearance by ethanolic extracts of Caulerpa lentillifera against Parkinson's disease pathology

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Abstract: Therapeutic effects of diverse bioactive compounds from marine derived extracts against Parkinson's disease (PD) through mechanisms such as antioxidant and inhibition of alpha-synuclein aggregation have been promising complementary, multi-target approaches for their neuroprotective potential. *Caulerpa lentillifera* (sea grape) ethanolic extracts (CLET) contain potent bioactive compounds, including phenolic compounds, flavonoids, and tannins and possess a high antioxidant capacity and low toxicity. This study demonstrated the potential of CLET against PD pathologies, primarily by activating the Keap1-Nrf2 (nuclear factor erythroid 2-related factor 2)-ARE pathway. By upregulating Nrf2, these extracts reduce oxidative stress and mitigate alpha-synuclein aggregation, a key hallmark of PD. *In vitro* study, the human neuroblastoma cell line (SH-SY5Y) was incubated with 1-Methyl-4-phenylpyridinium (MPP+) with or without CLET. *In vivo* study (n=5/group*)*, male ICR mice were orally administered CLET (50 mg/kg) for 17 days and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (30 mg/kg, 12-hour intervals) during the last 7 days. Western blot analysis showed that CLET significantly reduced alpha-synuclein expression *in vivo* ($p < 0.01$) and *in vitro* ($p < 0.05$). *In vitro*, CLET elevated the nuclear translocation of Nrf2 and its downstream antioxidant genes, including Heme oxygenase 1 (HO-1) and Glutathione S-transferase (GST), which help neutralize toxic free radicals while restoring glutathione levels at $p < 0.001$. In addition, CLET significantly reduced MPP+-mediated cell death and apoptosis (MTT assay, $p < 0.001$) and restored mitochondrial membrane potential (MMP) by flow cytometry ($p < 0.01$). *In vivo*, CLET reduced neuronal loss in the substantia nigra ($p < 0.01$) and improved motor deficits in the open field, rotarod, and narrow beam tests ($p < 0.001$ to 0.01). In conclusion, currently available pharmacological therapies for PDs remain largely symptomatic and insufficiently address the molecular drivers of neurodegeneration, including Nrf2 modulators of oxidative stress and alpha-synuclein clearance. Exploring natural *C. lentillifera* extracts may yield synergistic agents alongside conventional therapies. These findings suggest that CLET may serve as a promising neuroprotective candidate for mitigating PD pathology through activation of the Nrf2 pathway and reduction of alpha-synuclein accumulation.

Disclosures: D. Rodma: None. **R. Sunan:** None. **S. Chompoopong:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.02/W12

Topic: C.03. Parkinson's Disease

Support: US Department of Education GAANN Fellowship P200A240048

Title: Role of berberine in modulating alpha synuclein aggregation through reactive oxygen species in transgenic Caenorhabditis elegans

Authors: *J. M. FLORES[1], Z. MATEO[2];
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Abstract: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide, characterized by the progressive loss of dopaminergic neurons. In PD, the misfolding and aggregation of α-synuclein disrupt vesicular transport and dopamine release, contributing to mitochondrial dysfunction and increased production of reactive oxygen species (ROS). Despite available treatments, many current therapies have been associated with increased ROS production, highlighting the need for alternative approaches that reduce oxidative stress and α-synuclein aggregation. This study aimed to evaluate the effect of berberine in Caenorhabditis elegans. Berberine is a natural alkaloid with reported antioxidant and neuroprotective properties. Synchronized L4-stage nematodes (NL5901 strain) was used to perform a toxicity assay with three concentrations (1 μM, 10 μM and 100 μM) of berberine to identify the least toxic dose. Subsequently, a ROS assay was conducted to quantify hydrogen peroxide levels as an indicator of oxidative stress following berberine exposure. The preliminary results showed that 10 μM berberine is the least toxic concentration and it increases hydrogen peroxide levels compared to controls ($p<0.0001$). In conclusion, while berberine is characterized as an antioxidant, our preliminary findings demonstrate a contrasting capacity to elevate ROS levels. Future investigations utilizing fluorescence imaging are essential to validate these observations and elucidate the underlying mechanisms of action.

Disclosures: J.M. Flores: None. **Z. Mateo:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.03/W13

Topic: C.03. Parkinson's Disease

Title: A Novel Polyherbal Formulation Attenuates 6-Hydroxydopamine-Induced Parkinsonism via Modulation of BDNF/TrkB Signaling, α-Synuclein Pathology, Neuroinflammation, and Dopaminergic Homeostasis in Rats

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by nigrostriatal dopaminergic degeneration, oxidative stress, neuroinflammation, and α-synuclein

pathology. Current therapies provide symptomatic relief but do not halt disease progression, necessitating disease-modifying interventions. We previously developed and standardized a novel polyherbal formulation (PHF) comprising hydroalcoholic extracts of *Bacopa monnieri, Convolvulus prostratus, Asparagus racemosus,* and *Nigella sativa*, which demonstrated antioxidant, anti-inflammatory, and MAO-B inhibitory activities. This study evaluated the neuroprotective efficacy of PHF in a unilateral 6-hydroxydopamine (6-OHDA)-induced rat model of PD. Sixty adult male Sprague-Dawley rats were allocated into six groups (n=10): SHAM, 6-OHDA, L-DOPA/Benserazide (5/15 mg/kg), and PHF (50, 100, and 200 mg/kg, p.o.). Parkinsonism was induced by stereotaxic injection of 6-OHDA into the right medial forebrain bundle. Following a 21-day lesion period, animals received PHF for 28 days. 6-OHDA induced significant motor deficits, oxidative stress, neuroinflammation, dopaminergic depletion, and neuronal degeneration (###$p<0.001$). PHF dose-dependently improved motor coordination, balance, muscle strength, locomotor activity, and body weight, with significant effects at 100 and 200 mg/kg (***$p<0.001$). PHF restored glutathione, superoxide dismutase, and catalase levels while reducing malondialdehyde (**$p<0.01$, ***$p<0.001$). It also attenuated striatal TNF-α, IL-1β, and NF-κB levels, indicating suppression of neuroinflammation. HPLC analysis demonstrated restoration of dopamine and its metabolites (DOPAC and HVA), while PHF significantly increased BDNF and ATP levels (***$p<0.001$). RT-PCR revealed downregulation of α-synuclein and upregulation of tyrosine hydroxylase (TH) and dopamine transporter (DAT) gene expression. Histopathological findings confirmed preservation of nigrostriatal neuronal architecture. These findings demonstrate that PHF exerts neuroprotective effects through attenuation of oxidative stress and neuroinflammation, restoration of dopaminergic homeostasis, enhancement of neurotrophic support and mitochondrial function, and modulation of PD-related molecular markers, supporting its potential as a multi-target therapeutic candidate for PD.

Disclosures: K. Rathod: None. **U. Aswar:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.04/W14

Topic: C.03. Parkinson’s Disease

Title: IDENTIFICATION AND VALIDATION OF POTENTIAL TARGETS FOR ALPHA SYNUCLEIN PATHOLOGY MODULATION

Authors: *L. STRID ORRHULT[1], S. JANUTENAS[2], A. JÄMSÄ[2], S. KILPINEN[3], P. KARILA[1], A. VUORENPÄÄ[4], A. DOMANSKYI[5], M. T. AIRAVAARA[6], V. STRATOULIAS[7], J. PIHL[1];
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Abstract: Insoluble aggregates (Lewy bodies) consisting of misfolded alpha-synuclein (αSyn) accumulate in the nervous system of most Parkinson's disease (PD) patients. This process can affect multiple cellular functions, eventually leading to neuronal death. Despite the growing prevalence of the PD, there are currently no disease modifying therapies.
Based on literature evidence, a phenotypic screen with lentiviral shRNA vectors was performed to identify potential targets capable of modulating p-αSyn-129 pathology in post-mitotic primary neurons. Mouse primary cortical and dopaminergic cultures were treated with lentiviral shRNAs to knock down 20 selected targets using 4 different oligos for each target and later treated with pre-formed fibrils (PFFs) to induce the p-αSyn-129 pathology. After 14 days in vitro, cultures were fixed and immunofluorescent staining performed to evaluate neuronal health, p-αSyn-129 pathology, lysosomal health and function. Additionally, dopamine secretion levels were measured longitudinally. Strictly standardized mean difference (SSMD)-based hit analysis was used to identify hits in primary screen (cortical neurons) while a 3-level mixed model statistical analysis was applied to the secondary screen (dopaminergic neurons). Primary screen classified 12 targets as hits for one or several oligos with some of them displaying dual effects depending on the oligo used. 4 lysosomal targets were selected for a secondary screen in dopaminergic neurons. Atp13a2 showed changes in p-αSyn-129 pathology and dopamine secretion without hindering neuronal health and was classified as a hit also in the secondary screen. Atp13a2 was then further investigated using pharmacological compound Vonoprazan and demonstrated effect on lysosomal function altering lysosomal marker levels. We conclude that our in vitro model is useful for identification and validation of targets involved in modulation of αSyn aggregation. Further characterization and more mechanistic studies can be performed in dopaminergic neurons where the results correlate well with the cortical cultures. Atp13a2 was classified as a hit in both culture systems as was also capable of altering dopamine secretions. With its role in lysosomal function, Atp13a2 makes a potential target for drug development with the aim of disease-modifying therapies in PD.

Disclosures: L. Strid Orrhult: A. Employment/Salary (full or part-time):; Cellectricon AB. **S. Janutenas:** None. **A. Jämsä:** None. **S. Kilpinen:** None. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Vuorenpää:** A. Employment/Salary (full or part-time):; Orion Pharma. **A. Domanskyi:** A. Employment/Salary (full or part-time):; Orion Pharma. **M.T. Airavaara:** None. **V. Stratoulias:** None. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.05/W15

Topic: C.03. Parkinson's Disease

Title: Endosulfine-alpha modulation of α-synuclein-membrane interactions: implications for reducing α-synuclein pathology in Parkinson's disease

Authors: *G. DRAFOR[1,2], C. CHANDRASEKARAN[1,2], T. HUANG[3], D. DATTA[3], K. J. WEBB[3], J.-C. ROCHET[1,2];
[1]Borch Dept. of Medicinal Chem. & Mol. Pharmacol, [2]Purdue Inst. for Integrative Neurosci., [3]Elmore Sch. of Electrical and Computer Engin., Purdue Univ., West Lafayette, IN

Abstract: Parkinson's disease (PD) is characterized by the formation and propagation of α-synuclein (aSyn) aggregates in the brain. aSyn adopts an amphipathic α-helical structure upon binding to phospholipid membranes - an interaction thought to be important for modulating vesicle trafficking and synaptic vesicle release - whereas dissociation from vesicles may favor its seed-induced aggregation into β-sheet-rich assemblies. Endosulfine-alpha (ENSA), a conserved cAMP-regulated phosphoprotein expressed in the CNS, binds directly to membrane-associated aSyn, and a phosphomimetic mutation at S109 (mimicking PKA phosphorylation) disrupts this interaction. Recently, we determined that ENSA alleviates seeded aSyn aggregation in rodent neurons or human iPSC-derived neurons exposed to aSyn preformed fibrils (PFFs). However, the mechanism by which ENSA inhibits aSyn seeded aggregation is unknown. We hypothesized that ENSA interferes with intracellular seeded aggregation by promoting aSyn-vesicle interactions. To test this hypothesis, we employed fluorescence lifetime imaging microscopy-Förster resonance energy transfer (FLIM-FRET) to assess the proximity between aSyn and endosomal vesicles. Primary rat cortical neurons and CRISPR-engineered, ENSA-deficient iPSC-derived neurons were transduced with adenoviral constructs encoding Rab5b fused to mTurquoise2 and aSyn fused to mVenus. In primary cortical neurons, the expression of wild-type ENSA, a phosphomimic mutant (S109E), or a phosphodeficient mutant (S109A) resulted in a significant decrease in mTurquoise2-Rab5 lifetime, indicating greater proximity between Rab5-containing early endosomes and aSyn-mVenus. Re-expression of wild-type ENSA or ENSA-S109A, but not ENSA-S109E, reduced mTurquoise2-Rab5 lifetime in ENSA-deficient human neurons.These findings suggest that ENSA promotes the association of aSyn with Rab5-containing early endosomal vesicles. Given the established role of ENSA as a membrane-associated aSyn binding partner, we propose a model in which ENSA enhances the localization or retention of aSyn at early endosomal membranes. Such an effect could limit the availability of aSyn for seeded aggregation in the cytosol by stabilizing membrane-bound aSyn in a non-pathogenic, α-helical state. Collectively, these results provide new insight into the molecular pathways through which ENSA modulates aSyn trafficking and pathology and support a role for ENSA in regulating early endosomal events relevant to PD progression.

Disclosures: G. Drafor: None. **C. Chandrasekaran:** None. **T. Huang:** None. **D. Datta:** None. **K.J. Webb:** None. **J. Rochet:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.06/W16

Topic: C.03. Parkinson's Disease

Support: NIH

Title: Microengineering Parkinson's Disease model to investigate vascular impairment and the pathological spread of α-synuclein

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Abstract: In Parkinson's disease (PD), α-synuclein (α-syn) pathology spreads across brain regions, yet the role of vascular dysfunction and blood-brain barrier (BBB) impairment in this disease propagation remains poorly understood. To address this, we developed a human midbrain-on-a-chip model that recapitulates PD-associated vascular impairment and enables the study of vascular contributions to α-syn pathology spread. Our tissue culture platform, fabricated from PDMS via soft-lithography, consists of a central neuron chamber, surrounding vascular channel, and side media channels (Fig. 1a). Differentiated neurospheres (dopaminergic neuronal cells) were co-cultured with self-assembled vascular networks (HUVECs and NHLFs in fibrin gel) to form a 3D vascularized midbrain tissue. Neurosphere differentiation was confirmed by βIII-tubulin, MAP2, and GAP43 expression, while CD31 staining verified vascular network formation (Fig. 1b). After establishment of neurovascular interactions, we introduced α-syn preformed fibrils (PFFs, 0.5 μM) into the vascular channel for 72 hours to model PD conditions. Results showed that PFFs-treated vessels exhibited increased permeability, with FITC-dextran leakage into extravascular space within 5 minutes, while controls remained intact (Fig. 1c). Immunofluorescence confirmed α-syn aggregation as punctate structures within neurospheres only after PFF treatment, indicating that intravascular fibrils crossed permeable vessels and induced endogenous α-syn aggregation (Fig. 1d). Moreover, PFF-treated devices displayed "string vessels" (thin, acellular structures) and reduced vascular integrity, indicating vascular pathology reported in PD patients (Fig. 1d). Here, we present a vascularized midbrain model that recapitulates the functional midbrain neurovascular unit and investigated propagation of α-syn pathology through compromised vascular networks, an aspect that remains largely underexplored.

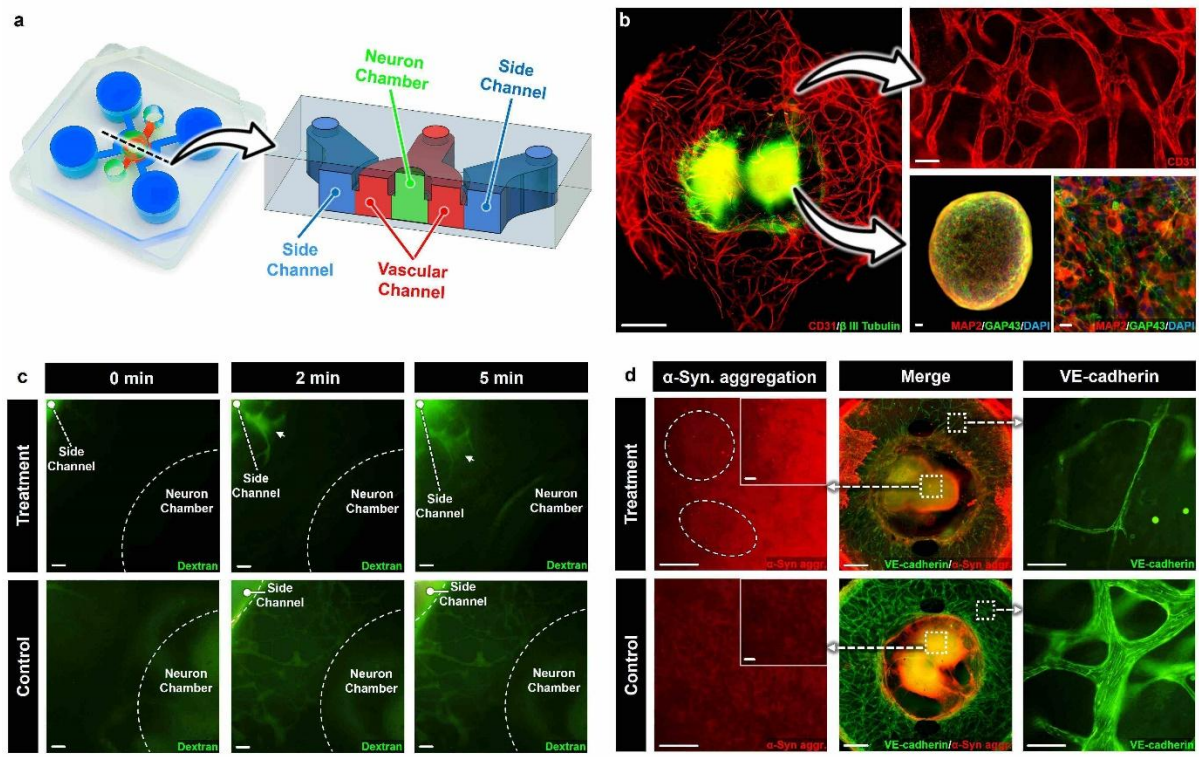


Fig. 1 Microengineered human mid-brain on a chip recapitulates α-synuclein-induced neurovascular pathology. **a)** Cross-sectional schematic of midbrain-on-a-chip shows the neuron chamber, vascular channel and side channels. **b)** Immunofluorescence analysis shows successful co-culture of vascular network (CD31) and differentiated neurospheroids (β III Tubulin) and the dendritic structures and axonal projections are observed by immunofluorescence of MAP2 (red) and GAP43 (green,) antibodies. Scale bars 1000 µm and 100 µm. **c)** FITC-dextran flow shows that in treated devices dextran leaked into the extracellular region over time. In control group dextran remain confined within the intravascular region during the same time period. Scale bar 100 µm. **d)** Immunofluorescence analysis of α-synuclein aggregation confirms the formation of pathological α-synuclein aggregates within neurospheroid and VE-cadherin shows disruption of endothelial cell junction following treatment. treated group shows positive puncta structure whereas no puncta structure observed in control group. Insets show magnified views of α-syn puncta within neurospheroid. Scale bars, 500 µm, 100 µm for main images and 25 µm for insets. Treated device shows fragmented, acellular vascular morphology and reduced VE-cadherin expression compared to control device. Scale bars 500 µm and 100 µm.

Disclosures: A. Alim: None. **J. Paek:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.07/W17

Topic: C.03. Parkinson’s Disease

Support: ASAP-027406

Title: Structural and biomechanical determinants of α-synuclein fibril propagation

Authors: *E. VIVERETTE[1], A. SOKRATIAN[1], A. B. WEST[2];
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Abstract: Synucleinopathies are defined by the accumulation and spread of misfolded α-synuclein (α-Syn) aggregates in the brain, including fibrillar α-Syn assemblies. Increasing evidence suggests that α-Syn fibrils can exist as structurally heterogeneous polymorphs across and within patients, but the biophysical properties that govern fibril growth, fragmentation, and pathogenic spread remain poorly understood. Our preliminary analyses of patient-derived α-Syn strain variants suggest that fibril brittleness, defined here as the tendency of fibrils to fragment into smaller seed-competent particles without disaggregating into monomer, varies substantially between patient-derived fibril preparations and is associated with fibril propagation. These findings suggest that brittleness may be an important determinant of α-Syn seeding activity and strain-dependent pathogenicity.

Drawing on break-and-release concepts established in prion biology, we hypothesize that fibril brittleness is an essential but poorly understood structural and biomechanical property that accelerates α-Syn fibrillation by increasing the number of seed-competent fibril ends. We further hypothesize that brittleness is influenced by molecular features of the fibril, including post-translational modifications, folding patterns, protofilament packing, and β-sheet organization. To test this hypothesis, we are characterizing Parkinson's disease-derived α-Syn fibrils using cryo-electron microscopy for structural determination and atomic force microscopy for biomechanical profiling. These studies will relate fibril architecture to mechanical features such as stiffness, fragility, and fragmentation propensity. Structural and biomechanical measurements will be integrated with functional assessments of fibrillation kinetics and seeding activity using real-time quaking-induced conversion assays.

Together, this work will test whether fibril brittleness provides a mechanistic link between α-Syn structure and propagation. These studies may help explain sources of strain heterogeneity in synucleinopathies and identify structural or biomechanical features of α-Syn fibrils that could be targeted to limit pathogenic spread.

Disclosures: E. Viverette: None. **A. Sokratian:** None. **A.B. West:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

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Topic: C.03. Parkinson's Disease

Support: UAEU Grant Support, Grant Code 12M214

Title: The Role of Parkin in Modulating α-Synuclein Pathology in a PFF-Induced Model of Parkinson's Disease.

Authors: *M. HAQUE[1], T. KITADA[3], M. ARDAH[4], N. RADWAN[2];
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Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the nigrostriatal pathway and the accumulation of misfolded alpha-synuclein (α-syn). Aggregated α-syn forms Lewy bodies that induce cellular stress, mitochondrial dysfunction, and neuronal death. Using a pathogenic model in which wild-type α-synuclein preformed fibrils (PFFs) initiate the propagation of endogenous α-syn, we previously demonstrated that this process is significantly exacerbated when PFF-injected mice are challenged with a low dose of MPTP (10 mg/kg body weight). In the present study, we investigated the capacity of Parkin overexpression to influence α-syn aggregation, post-translational modification, and propagation.Custom adeno-associated viral vectors expressing human Parkin (AAV-Parkin) or a GFP control were generated and validated in vivo. Robust Parkin overexpression in the substantia nigra pars compacta (SNc) was confirmed by immunostaining and Western blot analysis. In animals overexpressing Parkin, the aggregation pattern of α-syn appeared to shift markedly toward the stable tetrameric form, while significantly lower levels of filamentous and monomeric α-syn were observed compared with the GFP-treated counterparts. The size of phosphorylated α-syn (pS129) inclusions colocalized with tyrosine hydroxylase (TH)-positive neurons in the SNc was also significantly reduced. Dot blot analysis further demonstrated decreased levels of toxic filamentous α-syn species. Biochemically, Parkin expression increased ubiquitin levels, elevated dimeric BCL-2, and altered the distribution of α-syn species, suggesting enhanced protein quality control and anti-apoptotic signaling. However, TH immunostaining in the Parkin-expressing SNc region exhibited high background staining, which interfered with accurate quantification of TH-positive neurons and warrants further investigation.

Disclosures: M. Haque: None. **T. Kitada:** None. **M. Ardah:** None. **N. Radwan:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

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Program #/Poster #: PSTR263.09/W19

Topic: C.03. Parkinson’s Disease

Support: MJFF-028012

Title: Modelling Alpha-Synuclein Aggregation in a Human iPSC-Derived Dopaminergic Neuron culture system

Authors: *M. ZANELLA[1], X.-X. LIN[1], **C. J. M. LOOMANS**[1], F. STEVENHAGEN[1], N. POLINSKI[2], M. BSIBSI[1], A.-M. ZUURMOND[1];
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Abstract: Human induced pluripotent stem cell (iPSC)-derived models are increasingly central to neurodegenerative drug discovery, offering scalable and human-relevant systems that improve

target validation and reduce translational failure. In Parkinson's disease (PD) and related synucleinopathies, high clinical attrition rates are often attributed to the limited predictive power of traditional cell and animal models, underscoring the need for more physiologically relevant platforms. Here, we developed a physiologically relevant iPSC-derived dopaminergic neuron model to promote α-synuclein (α-syn) aggregation and phosphorylation—key pathological hallmarks of PD. iPSC-derived neuronal lines were evaluated and selected based on cell health, morphology, and endogenous expression levels of α-syn and tyrosine hydroxylase (TH), a dopaminergic neuron marker, using high-content imaging and ELISA read-outs. Within 2-3 weeks in culture, a homogeneous population of dopaminergic neurons was established, with over 80% TH-positive and 60% α-syn-positive cells. In this model, α-synuclein (α-syn) pathology was induced through exposure to preformed fibrils (PFFs), providing a clinically relevant trigger of disease pathology. Conditions were optimized for concentration and exposure times. In parallel, a complementary model was developed to assess PD-associated mitochondrial dysfunction through TOM20-based mitochondrial profiling in iPSC-derived dopaminergic neurons. To enhance both assay complexity and biological relevance, advanced model configurations were evaluated, leading to the development of neuron-astrocyte co-culture systems that more accurately recapitulate disease-relevant cellular interactions. Collectively, these models provide robust and physiologically relevant platforms suitable for high-throughput screening and mechanistic studies, supporting therapeutic development for PD and other synucleinopathies. Furthermore, these in vitro systems reduce reliance on animal studies, aligning with the 3Rs principles of ethical research.

Disclosures: M. Zanella: None. **X. Lin:** None. **C.J.M. Loomans:** None. **F. Stevenhagen:** None. **N. Polinski:** None. **M. Bsibsi:** None. **A. Zuurmond:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.10/W20

Topic: C.03. Parkinson's Disease

Title: siRNA Targeting SNCA Alleviates Pathology and Motor Deficits in a Rat Parkinson's Model Induced by AAV-α-Syn/PFF

Authors: *Y. WANG[1], J. TAN[2], **L. ZHANG**[3];
[1]WuXi AppTec, Shanghai, China; [3]IVPU, [2]WuXi AppTec, Qidong, China

Abstract: siRNA Targeting SNCA Alleviates Pathology and Motor Deficits in a Rat Parkinson's Model Induced by AAV-α-Syn/PFF Yumeng Wang[1], Lifeng Zhang[1], Dihang Lin[1], Jun Zhou[2], Andy Ng[1], Juan Tan[1]1.WuXi Biology, WuXi AppTec, China2.WuXi TIDES, WuXi AppTec, China
Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the accumulation and spread of misfolded α-synuclein (α-Syn), leading to dopaminergic neuronal

loss, neuroinflammation, and motor dysfunction. Targetingα-Syn represents a promising therapeutic strategy for PD. In this study, we investigated the therapeutic potential of SNCA siRNA in a rat model induced by AAV-mediated human wild-type α-Syn overexpression plus α-Syn preformed fibril (PFF) seeding in the substantia nigra pars compacta. Motor function impairment was confirmed by the cylinder test which revealed significant forelimb asymmetry indicative of unilateral nigrostriatal dysfunction. Animals were grouped based on baseline behavioral performance to ensure comparable disease severity prior to treatment.SNCA siRNA was administered after model establishment, and therapeutic efficacy was evaluated at 4- and 8-weeks post-treatment using a comprehensive motor behavioral assessment battery, including the cylinder test, rotarod, pole test, and apomorphine-induced rotation. Model animals exhibited robust and progressive motor deficits across all assessments, whereas SNCA siRNA-treated animals demonstrated consistent and time-dependent functional improvement.Mechanistically, SNCA siRNA significantly reduced SNCA mRNA expression in brain tissue. LC-MS/MS analysis showed restoration of striatal dopamine levels. Immunofluorescence staining further demonstrated reduced α-Syn aggregation, preservation of tyrosine hydroxylase (TH)-positive dopaminergic neurons, and marked attenuation of astrocytic and microglial activation, suggesting suppression of neuroinflammatory responses.These findings demonstrate that SNCA siRNA confers disease-modifying effects in this clinically relevant PD model by alleviating α-Syn pathology, restoring dopaminergic function, and improving motor performance. Our results support the therapeutic potential of SNCA-targeted RNA interference for Parkinson's disease.**Keywords:** Parkinson's disease; α-synuclein pathology; SNCA siRNA; AAV-α-Syn /PFF rat model; dopaminergic dysfunction; neuroinflammation

Disclosures: Y. Wang: None. **J. Tan:** None. **L. Zhang:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

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Program #/Poster #: PSTR263.11/W21

Topic: C.03. Parkinson's Disease

Support: SFB 1690
SFB 1286

Title: Oligomeric alpha-synuclein profiling for accessible Parkinson's disease diagnosis

Authors: *D. KRAH[1], A. NTOLKERAS[1], S. H. CHANDA[1], B. MOLLENHAUER[2,3], S. O. RIZZOLI[1], A. H. SHAIB[1];
[1]Neuro- and Sensory Physiol., [2]Neurol., Univ. Med. Ctr. Göttingen, Göttingen, Germany; [3]Neurol., Paracelsus-Elena-Klinik, Kassel, Germany

Abstract: The diagnosis of most neurodegenerative diseases, including Parkinson's disease, often occurs late, as compensatory mechanisms across neuronal networks and molecular

pathways can mask definitive clinical symptoms. Consequently, current treatment remains largely symptomatic and has a limited impact on disease progression. Recent advances in alpha-synuclein detection, including ELISA-based measurements of aggregated alpha-synuclein and FDA-approved Seed Amplification Assays (SAAs) for aggregation-competent alpha-synuclein in cerebrospinal fluid (CSF), have strengthened molecular support for diagnosis. However, these approaches do not quantitatively resolve the aggregation species most informative for early diagnosis and disease monitoring. Alpha-synuclein aggregates occur in a broad range of sizes and morphologies, from small oligomers to larger assemblies, requiring super-resolution imaging. One-Step Nanoscale Expansion (ONE) microscopy fills this gap by combining expansion microscopy with fluorescence fluctuation analysis, enabling scalable confocal imaging at single-nanometer resolution with relatively low demands on equipment, expertise, and time. Using ONE microscopy on CSF, we previously showed that Parkinson's disease patients and controls differ not simply in total aggregate burden, but in the relative abundance of the smallest oligomeric alpha-synuclein species. Despite this promise, CSF collection is invasive and unsuitable for routine testing or long-term monitoring. This creates a need to identify more accessible samples that can report alpha-synuclein aggregation with comparable diagnostic value. Alpha-synuclein has been detected in saliva, urine, blood, tears, colon and skin, raising the possibility that peripheral samples contain disease-relevant species. This project aims to identify which accessible sample types can serve as practical alternatives to CSF by quantifying aggregate load, visualizing and classifying aggregate species, and comparing Parkinson's disease patients with controls. Preliminary results indicate an increased oligomeric fraction of alpha-synuclein in Parkinson's disease patients, supporting the feasibility of ONE microscopy-based aggregate profiling for accessible biomarker discovery and disease monitoring.

Disclosures: D. Krah: None. **A. Ntolkeras:** None. **S.H. Chanda:** None. **B. Mollenhauer:** None. **S.O. Rizzoli:** None. **A.H. Shaib:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.12/W22

Topic: C.03. Parkinson's Disease

Title: Widespread synucleinopathy in an aged mouse model of Parkinson's disease : insights from histology and spatial omics.

Authors: *N. CALLIZOT[1], G. CULLEY[1], G. FLOWER[1], V. DE CASTRO[1], A. WOJCINSKI[1], A. HENRIQUES[2];
[1]Neuro-Sys, Gardanne, France; [2]Neuro-Sys, GARDANNE, France

Abstract: Background The major pathological hallmarks in Parkinson's disease (PD) include loss of dopaminergic neurons due to widespread intracellular alpha-synuclein (α-Syn) inclusions and Lewy bodies aggregates. α-Syn is a structural protein particularly abundant in dopaminergic

neurons where it is mainly located at the presynaptic terminal and involved in synaptic activity and function. Lysosomal dysfunctions are now well known to be key elements in pathogenesis. Mutations on the lysosomal enzyme GBA is a strong risk factor for PD. **Methods** α-Syn preformed fibrils (PFFs) were injected in the substantia nigra of aged mice. Conduritol B epoxide was given (i.p.; 3x per week) to partially inhibit GBA activity. Motor functions were assessed using automated system (Ladder test; Beam test). Four weeks after surgery, mice were deeply anesthetized, PBS and PFA perfused. Brains were collected and processed in paraffin. Xenium-based spatial transcriptomic analysis, using the mouse brain panel, was used to assess cellular processes activated in neurodegeneration such as lysosomal, mitochondrial and inflammatory pathways, at the single cell level. Spreading of alpha-synuclein aggregates and phosphorylated alpha-synuclein were assessed by histology. **Results** Alpha-synuclein aggregation and phosphorylation was evidenced at the direct site of injections, in the substantia nigra, and also in the striatum. SpatialOmics analysis revealed massive activation of microglia cells, cellular stress and dysregulation of the lysosomal pathway, along the nigro-striatal tractus. **Conclusions** Gathering spatial transcriptomic data, combined with histology, has further validated the neurodegenerative disease-like phenotype of an induced model of Parkinson's disease, combining aged, inhibition of GBA and toxicity of alpha-synuclein, revealing pathological mechanisms involved. Moving forward, this data will allow us to investigate these mechanisms to better understand neurodegenerative processes.

Disclosures: N. Callizot: None. **G. Culley:** None. **G. Flower:** None. **V. de Castro:** None. **A. Wojcinski:** None. **A. Henriques:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.13/W23

Topic: C.03. Parkinson's Disease

Title: A new model for human alpha synuclein overexpression in Drosophila

Authors: *K. ROSIKON[1], A. ATHEBY[2], A. BROWN[1], Z. JENKINS[1], B. GAMBLEMCQUEEN[4], J. LATIMORE[5], H. O. LAWAL[3];
[2]Biol. Sci., [3]Biol., [1]Delaware State Univ., Dover, DE; [4]Xavier Univ. of Louisiana, New Orleans, LA; [5]Florida A&M Univ., Tallahassee, FL

Abstract: Parkinson's Disease (PD) is progressive neurodegenerative movement disease characterized by loss of dopaminergic innervations primarily in substantia nigra pars compacta. On a cellular level, a-synuclein (α-syn) misfolding and its aggregation make up a key component of Lewy Bodies (LBs) and Lewy neurites, first-identified and main genetic and neuropathological hallmark for developing PD. Although complement fly constructs are already available, the challenges remain in identifying a robust α-syn model that adequately mimics PD pathology and elucidates the subcellular function of the protein. Therefore, we sought to develop

the novel construct for studying α-syn pathology in *Drosophila*. This model allows to track α-syn localization in dopaminergic neurons and subsequently identify the protein's aggregation dynamics and its expression in vivo and in vitro. Here, we present the identification and characterization of three independent transgenic α-syn overexpressor lines with red fluorescent protein inserted at the C-terminal tail. We report that neither pan-neuronal nor DA-specific overexpression of human α-syn has a major effect on organismal survival in males and females of at least two independent lines. Moreover, we show an age-dependent decrease in locomotion in the α-syn overexpressing flies. We also report preliminary results on the state of phosphorylated α-syn (at the Ser129 site) in young and old overexpressors. Taken together, our data shows that these lines reproduce key behavioral features of familial PD and could inform future studies aimed at utilizing the characterized α-syn overexpression constructs as a genetic model to test the efficacy of putative anti-PD drugs in our collection.

Disclosures: K. Rosikon: None. **A. Atheby:** None. **A. Brown:** None. **Z. Jenkins:** None. **B. Gamblemcqueen:** None. **J. Latimore:** None. **H.O. Lawal:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.14/W24

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01MH133608

Title: Electrophysiological impact of cell-type specific α-synuclein aggregation on serotonergic neurons of the raphe

Authors: *M. B. CORNIQUEL, M. WALLACE;
Anat. and Neurobio., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: The presence of α-synuclein (α-syn) dense Lewy bodies in the mid-brain corresponds with a loss of dopamine neurons and the onset of motor symptoms in patients with Parkinson's disease (PD). The impact of Lewy body formation in other neuronal subtypes and how this relates to PD symptoms, however, remains poorly understood. We constructed and validated a novel Flp-recombinase dependent adeno-associated virus (AAV) for the selective overexpression of α-syn (AAV-fDIO-SNCA-Myc) in a cell-type specific manner. Injection of this AAV into the raphe nuclei of transgenic mice (ePet-Flp) expressing Flp-recombinase in serotonergic neurons allows us to explore the specific impact of Lewy bodies within this circuit without the potential confound of dopaminergic neuronal loss. Expression is seen almost exclusively in tryptophan hydroxylase (TPH2) expressing cells at 5-weeks (95.3%) and 10-weeks (95.8%) post-injection. This represented 40.9% of detected TPH2 neurons at 10 weeks post-injection. Widefield imaging of GRAB 5-HT3.0 signal intensity in a downstream structure (lateral habenula) shows a reduction in serotonin release in response to electrical stimulation (40μA) following 9-11 weeks

of α-syn overexpression. This reduction in signal intensity scales with the frequency (1 - 40 Hz) of stimulation, indicating greater impairment in serotonin release during periods of intensive vesicle cycling and release. Through whole-cell patch-clamp slice electrophysiology, we also seek to characterize if 10 weeks of α-syn overexpression alters the passive and active membrane characteristics of serotonergic neurons, as compared to control viral vectors. This novel viral tool and the described experiments aid in our understanding of non-dopaminergic circuit dysfunction in Parkinson's disease and may provide additional mechanistic targets for therapeutic treatments and improve treatment outcomes for patients.

Disclosures: M.B. Corniquel: None. **M. Wallace:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.15/W25

Topic: C.03. Parkinson's Disease

Support: U01 NS128433

Title: Cerebrospinal Fluid Proteomic Signatures Enable Molecular Classification Across the Parkinson's Disease and Lewy Body Disease Spectrum

Authors: *M. SESHADRI;
Emory Univ., Atlanta, GA

Abstract: Parkinsonism comprises a heterogeneous group of neurodegenerative disorders characterized by cardinal motor features, including bradykinesia, rigidity, resting tremor, and postural instability. While Parkinson's Disease (PD) represents the most prevalent form, the spectrum extends to related synucleinopathies, including Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia. These conditions are unified by the pathological aggregation of misfolded α-synuclein within neuronal inclusions (Lewy bodies), which contributes to progressive synaptic dysfunction, neuronal loss, and network-level impairment. Despite shared pathology in the Lewy body disease (LBD) spectrum, substantial heterogeneity exists in cognitive involvement, disease progression, and therapeutic response. Accurate early diagnosis remains challenging due to overlapping clinical features, particularly among patients presenting with cognitive impairment and other non-motor manifestations. The identification of molecular biomarkers reflecting underlying α-synuclein pathology is therefore critical for improving diagnostic precision and patient stratification for clinical and therapeutic applications.
To address this gap, we analyzed cerebrospinal fluid (CSF) proteomic data from the Parkinson's Disease Biomarkers Program (PDBP), a multi-institutional biorepository supported by the National Institutes of Health. The study included 685 CSF samples from controls, patients with PD, and patients with DLB.
Proteomic profiling was performed using data-independent acquisition mass spectrometry (DIA-

MS) on a trapped ion mobility spectrometry time-of-flight platform (timsTOF). Differential expression analyses were conducted across multiple biologically and clinically relevant comparisons to identify proteins associated with disease status, cognitive impairment, and α-synuclein pathology.
Our findings support the feasibility of constructing a disease-discriminative protein expression matrix capable of differentiating subtypes across the LBD spectrum. Such molecular classification frameworks have the potential to substantially improve early and accurate diagnosis, particularly in clinically ambiguous cases. Furthermore, the high-throughput nature of DIA-MS on the timsTOF platform enables scalable, reproducible proteomic profiling, facilitating large-cohort analyses and accelerating biomarker discovery. This integrative approach provides a foundation for the development of robust, clinically translatable diagnostic tools and advances efforts toward precision medicine in neurodegenerative disease.

Disclosures: M. Seshadri: None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.16/W26

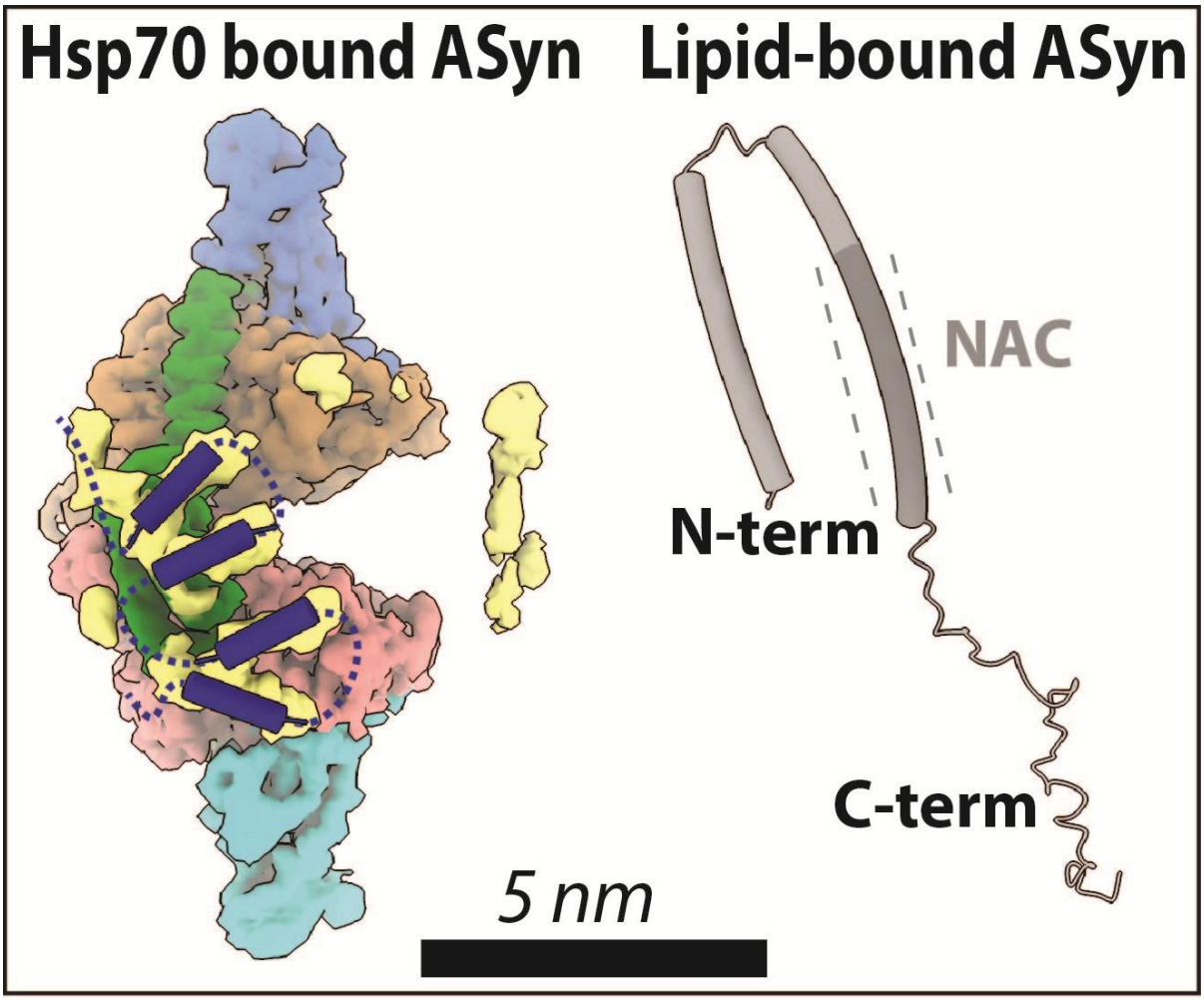
Topic: C.03. Parkinson’s Disease

Title: A Novel alpha-Synuclein Conformation Captured in Complex with Hsp70 by Cryo-EM

Authors: *P. TSIOLAKI[1,2], W. SADOWSKA[4], M. TABIOS[4], E. TSE[5], D. SOUTHWORTH[3], D. AGARD[4,6], L. C. MCCONLOGUE[4];
[1]Dept. of Biochem. and Biophysics, Univ. of Calilfornia San Francisco, San Francisco, CA; [2]Dept. of Biochem. and Biophysics, [3]Inst. for Neurodegenerative Dis. and UCSF Weill Inst. for Neurosciences, Univ. of California at San Francisco, San Francisco, CA; [4]Dept. of Biochem. and Biophysics, [5]Inst. for Neurodegenerative Dis. and UCSF Weill Inst. for Neurosciences, Univ. of California San Francisco, San Francisco, CA; [6]The Chan-Zuckerberg Inst. for Advanced Biol. Imaging, Redwood City, CA

Abstract: Neuropathological, biochemical, and genetic evidence implicates progressive α-synuclein (ASyn) misfolding in the emergence and onset of Parkinson’s disease (PD) and related synucleinopathies. In cell and animal models, increased levels of the stress-inducible chaperone Hsp70 protect against ASyn-associated neurodegeneration, an effect generally attributed to its conventional promiscuous mode of action utilizing Hsp70’s well-understood ATP-cycling mechanism. This assumption has stymied the development of therapies capitalizing on Hsp70’s protective ability. Our results contradict the conventional view by showing that Hsp70 suppresses the earliest and most neurotoxic stage of ASyn oligomerization through a previously unidentified interaction site distinct from its canonical client-binding site (Tao, J., PMCID: PMC8102405, Abstract McConlogue et al.). Using cryo-EM, we resolved the structure of monomeric ASyn bound to dimers of human ATP-bound Hsp70. ASyn engages a surface on the

outside of the closed substrate-binding domain lid (SBD-lid) that is distinct from the canonical substrate-binding site, revealing a non-canonical interaction mechanism. Analysis of Hsp70 deletion mutants indicates that the lid domain involved in ASyn recognition is crucial for blocking ASyn oligomerization and is distinct from the canonical substrate-binding region that interacts with NR peptide inhibitor. Although monomeric ASyn is intrinsically disordered and is known to acquire a stable structure only in membrane-associated states, we found that Hsp70 binding induces a previously unknown ASyn conformation containing multiple short α-helices unlike any prior characterized ASyn structures (see figure). Together, these observations suggest that Hsp70 prevents ASyn oligomerization by facilitating a novel structured conformation that sequesters regions required for oligomer formation and provides opportunities for therapeutic targeting of Hsp70 to ASyn.



Disclosures: P. Tsiolaki: None. **W. Sadowska:** None. **M. Tabios:** None. **E. Tse:** None. **D. Southworth:** None. **D. Agard:** None. **L.C. McConlogue:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.17/W27

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Van Andel Institute MiND pilot grant

Title: Dimerisation and twist reversal of the Lewy fold in alpha-synuclein mutants with Parkinson's disease and dementia

Authors: *Y. YANG;
Structural Biol., Van Andel Res. Inst., Grand Rapids, MI

Abstract: Dominantly inherited missense and gene dosage mutations in *SNCA*, the α-synuclein gene, cause familial forms of Parkinson's disease and dementia. Here we report the structures of α-synuclein filaments from the brains of such individuals. Pathogenic mutations A53T and G51D in *SNCA* give rise to singlets and doublets of the Lewy fold with a left-handed helical twist in the absence of a peptide-like density for island A. By contrast, filaments from the non-pathogenic variant H50Q consist of singlets of the right-handed Lewy fold with a density for island A, like filaments of wild-type α-synuclein. The structures of filaments from homozygous mice transgenic for human mutant A53T α-synuclein (line M83) are unlike those from human brains. They are more similar to the multiple system atrophy folds than to the Lewy fold of Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies.

Disclosures: Y. Yang: None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.18/W28

Topic: C.03. Parkinson's Disease

Support: The Rogers Family Foundation
HHMI
EMBO ALTF 154-2020
NIH R21NS092897
NIH R21AG081779

Title: Hsp70 chaperone blocks α-synuclein oligomer formation via a novel engagement mechanism

Authors: *L. C. MCCONLOGUE[1], P. TSIOLAKI[2], M. TABIOS[3], D. AGARD[4];
[1]Univ. of California San Francisco, San Francisco, CA; [2]Dept. of Biochem. & Biophysics, Univ. of California at San Francisco, San Francisco, CA; [3]Univ. of California, San Francisco, San Francisco, CA; [4]Biochem. & Biophysics, Univ. of California, San Francisco, Burlingame, CA

Abstract: Neuropathological, biochemical, and genetic evidence implicates progressive alpha-synuclein (ASyn) misfolding in the emergence and onset of Parkinson's disease (PD) and related synucleinopathies. In cell and animal models, increased levels of the stress-inducible chaperone Hsp70 protect against ASyn-associated neurodegeneration, an effect generally attributed to its conventional promiscuous mode of action utilizing Hsp70's well understood ATP-cycling mechanism. Efforts to therapeutically exploit the protective role of induced Hsp70 have been stymied by the broad canonical action of Hsp70 on an array of critical cellular substrates and a lack of mechanistic understanding of how Hsp70 mediates ASyn protection. Our results contradict the conventional view by showing that human Hsp70 suppresses the earliest and most neurotoxic stage of ASyn oligomerization through a novel and unexpected mode of Hsp70 action (Tao, J., PMCID:8102405). We have developed biochemical assays to monitor the production of fibril seeding-competent low order ASyn oligomers in the absence of fibrillization. We show that Hsp70 blocks the formation of these ASyn oligomers in a manner that is independent of ATP state, does not require its nucleotide binding domain and is not perturbed by the canonical Hsp70 inhibitor, the NR peptide. Supporting this non-canonical mechanism, ASyn does not compete for NR binding to Hsp70. Thus, Hsp70 acts on ASyn using engagement that is separate from its canonical binding cleft. Using truncations, mutations and inhibitors, we confirm that Hsp70 interacts with ASyn via a non-canonical interaction site in the C-terminal domain that is separable from its canonical binding activity and separate from previously identified non-canonical Hsp70 engagement sites. We verify that a similar, non-canonical mechanism of Hsp70 blockage of ASyn oligomers is at play in H4 neuroglioma cells. Our new Cryo-EM structural data directly verify non-canonical Hsp70-ASyn engagement (see Abstract P. Tsiolaki et al.). We hypothesize that this non-canonical engagement is responsible for Hsp70's protective action in cell and animal models and in disease. Together, these findings suggest new therapeutic opportunities to target the Hsp70-ASyn interaction in PD and other synucleinopathies.

Disclosures: L.C. McConlogue: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dainton Biosciences, LLC. **P. Tsiolaki:** None. **M. Tabios:** None. **D. Agard:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.19/W29

Topic: C.03. Parkinson's Disease

Support: National Natural Science Foundation of China No. 82174468
Zhejiang Provincial Natural Science Foundation of China No. LZ24H250001

Title: When NK cells meet a novel autophagy inducer, α-synuclein aggregates collapse

Authors: ***Y. ZHANG**, Y. LIU;
Westlake Lab. of Life Sci. and Biomedicine, Hangzhou, China

Abstract: α-Synuclein aggregation-formed inclusions represent the primary pathological hallmark of Parkinson's disease (PD). These aggregates can propagate between neurons, exhibiting prion-like properties that render them extremely resistant to clearance—representing a major unmet gap in PD research. NK cells are important innate immune cells closely associated with the elimination of tumor cells and viral infections. Interestingly, precisely because of this characteristic, NK cells have been reported to effectively phagocytose extracellularly released α-synuclein aggregates (Earls RH, et al., PNAS, 2020). We are pleased to note that NKGen Biotech announced that its NK cell therapy SNK01 for PD has received IND approval from the U.S. FDA in 2024. Inspired by this, we sought to further enhance the therapeutic efficacy of NK cells against PD. Building upon our previous studies of a small-molecule compound, 4,4'-dimethoxychalcone (DMC) (Zhang WL, et al., Adv Sci, 2021; Gong JW, et al., Free Radic Biol Med, 2021), we further optimized to obtain a more potent autophagy inducer (designated as F-DMC). Using a high-throughput screening strategy by high-throughput sequencing (named by HTS2), we discovered that F-DMC can clear α-synuclein aggregates by promoting PINK1/Parkin-mediated mitophagy. By engineering NK cells to engraft F-DMC, this preparation effectively crosses the blood-brain barrier following intravenous administration. In the high-ROS environment of the PD model brain, the linkage between NK cells and F-DMC is cleaved, enabling the released NK cells to efficiently clear extracellular α-synuclein, while F-DMC eliminates intracellular α-synuclein, thereby ameliorating motor dysfunction and dopaminergic neuronal death in mouse models of synucleinopathies. This technology has also been granted patent protection, offering a promising new therapeutic strategy for PD.

Disclosures: Y. Zhang: None. **Y. Liu:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.20/W30

Topic:

Title: Molecular Insights into the Toxicity Linked with Three α-Synuclein Mutants (A18T, A29S, and A53V) that cause Parkinson’s Disease: Insights from Yeast.

Authors: ***S. CHANDAVIMOL**[1], J. PINAPALA[2], S. GACEK[3], S. K. DEBBURMAN[4];
[1]Neurosci., Lake Forest Col., Lake Forest, IL; [2]Lake Forest Col., Park City, IL; [4]Biol., [3]Lake Forest Col., Lake Forest, IL

Abstract: Parkinson’s Disease (PD) is the second most common neurodegenerative disorder, characterized by the death of midbrain dopaminergic neurons. This selective cell death is linked

with the misfolding and accumulation of the protein, α-synuclein. Six α-synuclein mutants previously linked to early-onset familial PD (A30P, E46K, H50Q, G51D, A53T, A53E) have been extensively studied for their mechanisms of toxicity. In contrast, three newer α-synuclein mutants linked to familial and sporadic PD (A18T, A29S, and A53V) are less well understood. We characterized these three mutants in well-established budding yeast (*S. cerevisiae*) model and found that A18T, A29S, and A53V are differentially toxic, with A53V being the most toxic, followed by A18T and A29S. The level of mutant toxicity correlates with α-synuclein aggregation, with A29S showing significantly less aggregation than the other two mutants. We also evaluated the combinatorial impact of double mutants (A18T/A29S, A29S/A53V, A18T/A53V) and a triple mutant (A18T/A29S/A53V). Our data shows that the A29S dominated over both A18T and A53V, significantly reducing their toxicities, indicating the importance of the A29 position, especially when combined with A53. Lastly, we assessed the effects of known α-synuclein post-translational modifications (acetylation, SUMOylation, nitration, and phosphorylation) on their toxicity by using either blocking/mimic mutants or yeast strains genetically altered for nitrative stress or SUMOylation. We report that: 1) acetylation broadly protects all three mutants; 2) SUMOylation also protects all three mutants and low levels make A29S quite toxic; 3) Nitration enhances A18T and A53V toxicity, but not A29S; and 4) surprisingly, phosphorylation at serine-87 protects all three mutants. Together, our findings in yeast helps us understand how each of these three rare mutants may generate mutant-specific neurotoxicity that underlies disease pathology.

Disclosures: S. Chandavimol: None. **J. Pinapala:** None. **S. Gacek:** None. **S.K. Debburman:** None.

Poster

PSTR263: Parkinson's Disease: Alpha-Synuclein

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR263.21/X1

Topic: C.03. Parkinson’s Disease

Support: ASBMB Undergraduate Research Award

Title: Molecular Analysis of α-Synuclein’s Mutation Hotspots Linked with Familial Parkinson’s Disease: Insights from Yeast

Authors: *K. E. FEIST[1], A. M. PEACOCK[1], S. GACEK[1], S. K. DEBBURMAN[2];
[2]Biol., [1]Lake Forest Col., Lake Forest, IL

Abstract: Parkinson’s Disease (PD) is the second most common neurodegenerative disorder. PD involves the selective death of midbrain, dopaminergic neurons in the substantia-nigra and the formation of Lewy Bodies. The selective death of these cells is linked with the misfolding and accumulation of the fibrous, 140 amino acid protein, α-synuclein. Early-onset PD has been attributed to several inherited and sporadic mutations on α-synuclein. Interestingly, many of

these mutations cluster within select regions of α-synuclein, two of which are the 29-30 and 50-53 amino acid segments. These two segments independently gave rise to eight independent, natural mutations: A29S, A30P/G and H50Q, G51D, A53T/E/V. Using our budding yeast (*S. cerevisiae*) model, we characterize both the individual mutations as well as extend beyond by examining these two α-synuclein mutation "hotspots" regionally. We assessed 1) the toxicity, localization and expression of the individual natural mutations that appear in the 29-30 and 50-53 amino acid segments 2) the effects on α-synuclein toxicity and aggregation when combining the natural mutations at each hotspot and 3) properties of the individual amino acids at the A29, A30 and A53 natural mutant sites that are key to each site's toxicity. We also performed a qualitative analysis of α-synuclein's structure with the hotspot mutations using the AlphaFold AI's structural analysis program. We report that 1) the individual, natural mutations at the hotspots display varying degrees of toxicity. Natural mutations at the 50-53 site all appear toxic with the exception of G51D, while natural mutations at the 29-30 site, A29S and A30P, are less toxic with the exception of A30G. 2) Combining natural mutations at hotspots reduces toxicity to that of the least-toxic individual mutation in the combination. Finally, 3) acidic amino acid substitutions tend to reduce the toxicity of mutants, while basic and highly hydrophobic substitutions tend to retain or induce greater toxicity at both sites. We are currently assessing how the 28th and 31st positions that flank the 29-30 segment influence α-synuclein toxicity. Together, our findings aid in understanding how mutations in these select regions of α-synuclein may generate neurotoxicity that can explain underlying disease pathogenesis and may predict related genetic predisposition to PD based on genetic sequences in this region.

Disclosures: K.E. Feist: None. **A.M. Peacock:** None. **S. Gacek:** None. **S.K. Debburman:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.01/X2

Topic: C.03. Parkinson's Disease

Support: Beneva Anxiety Research Fund 2025-04

Title: Positive correlation between cerebellar-amygdalar functional connectivity and anxiety in Parkinson's Disease: A pilot study

Authors: *T. PARKER[1], A. KARIMI[2], J. F. DESOUZA[2];
[2]Psychology, [1]York Univ., Toronto, ON, Canada

Abstract: Anxiety is an overlooked and understudied symptom of Parkinson's Disease (PD), a neurodegenerative disorder primarily characterised by motor deficits. Previous research by Zhang et al. (2024) has shown reduced functional activation between the dentate nucleus and the amygdala in patients with bipolar disorder and high co-morbid anxiety. Their work also shows

that exercise mediates anxiolysis by acting on this circuit. The goal of our study is to investigate the relationship between anxiety and this circuit of interest in people with Parkinson's Disease to better understand the underlying circuitry where altered connectivity is both prevalent and poorly understood. We analyzed resting-state functional magnetic resonance imaging from the Parkinson's Precision Medicine Initiative (PPMI) database and correlated it with the state-trait anxiety inventory assessment. Though we initially hypothesized a negative correlation consistent with the results from Zhang et al. (2024), our analysis found a significant positive correlation between the functional connectivity of the cerebellar and amygdalar nuclei and sessional anxiety scores whilst controlling for overall anxiety scores ($r = 0.51$, $p = 0.017$, $n = 21$). These participants were selected approximately evenly from the highest and lowest scores across the spectrum of anxiety results in the database. This study is the first to look for this relationship between the cerebellum and the amygdala in humans with PD. The next phase of research will analyze exercise/dance data for a larger group of participants to observe the effect of physical activity on anxiolysis within this circuit, and has the potential to provide evidence for the use of exercise/dance as a rehabilitation method beyond motor dysfunction.

Disclosures: T. Parker: None. **A. Karimi:** None. **J.F. DeSouza:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.02/Web Only

Topic: C.03. Parkinson's Disease

Support: APDA/D07
ALF is a scholarship holder (1222481) from SECIHTI

Title: Protective Role of Cognitive Reserve in the cognition of patients with Parkinson's disease

Authors: *A. LÁZARO-FIGUEROA[1], A. MORALES DE ARCIA[2], I. ESTRADA-BELLMANN[7], Y. MATUK PEREZ[8], C. GUERRA GALICIA[9], N. GANDARILLA MARTINEZ[10], U. CABALLERO SANCHEZ[11], E. MORELOS[12], P. REYES[3], A. MEDINA-RIVERA[3], J. ESQUIVIAS[4], S. ALCAUTER[5], M. E. RENTERÍA[13], A. RUIZ-CONTERARAS[6]; [1]Lab. de Neurogenómica Cognitiva, Facultad de Psicología, Univ. Nacional Autonoma de Mexico, Mexico, City, Mexico; [2]Lab. de Neurogenómica Cognitiva, Facultad de Psicología, Univ. Nacional Autónoma de México, Tuxtla, Mexico; [3]Lab. Internacional de Investigación sobre el Genoma Humano, [4]Univ. Nacional Autónoma de México, Querétaro, Mexico; [5]Neurobiología Conductual y Cognitiva, Univ. Nacional Autónoma de México, Queretaro, Mexico; [6]Lab. de Neurogenómica Cognitiva, Facultad de Psicología, Univ. Nacional Autónoma de México, Mexico City, Mexico; [7]Movement Disorders Clinic, Neurol. Division, Intrnl. Med. Dept., Univ. Hosp. "Dr. José E. González", Univ. Autónoma de Nuevo León, Monterrey, Mexico; [8]Facultad de Medicina, Univ. Autónoma de Querétaro, Querétaro, Mexico; [9]Neurociencias PRISMA AC, San Luis Potosí, Mexico; [10]Ctr. Neurológico del Ctr. Médico

ABC, Ciudad de México, Mexico; [11]INMEGEN, Mexico City, Mexico; [12]Hosp. Regional ISSSTE, Morelia, Mexico; [13]Brain & Mental Hlth. Program, QIMR Berghofer Med. Res. Inst., Herston, Australia

Abstract: Background: Mild cognitive impairment (MCI) is a prevalent non-motor feature of Parkinson's Disease (PD), with substantial variability in its presentation. This study investigated the protective role of Cognitive Reserve (CR) in the presence of MCI.
Methods: A cross-sectional analysis comparing PD patients and healthy controls. Cognition was evaluated through the Montreal Cognitive Assessment and the Creyos Battery. CR was measured by a composite index including education, occupational experience (CR-OE), and leisure engagement (CR-LE). Based on MoCA scores, the sample was segregated among three groups: Control normal cognition (C-NC), PD patients with normal cognition (PD-NC), and PD patients with MCI (PD-MCI). Multinomial and binomial logistic regressions were performed to assess whether the presence of MCI was predicted by age, years of education, CR-OE, CR-LE, the PD severity, and years with PD.
Results: Higher CR-LE was a significant protective factor: each one-unit increase in CR-LE score reduced the odds of classification as PD-NC by 2% (OR = 0.98) and as PD-MCI by 5% (OR = 0.95) relative to healthy controls ($p<0.001$); this protective effect persisted within the PD group alone (OR = 0.98, $p<0.001$).
Conclusions: Higher CR-LE seems to be a robust protective factor that may delay cognitive decline. These findings support CR-focused lifestyle interventions.

Disclosures: A. Lázaro-Figueroa: None. **A. Morales de Arcia:** None. **I. Estrada-bellmann:** None. **Y. matuk perez:** None. **C. Guerra Galicia:** None. **N. Gandarilla Martinez:** None. **U. Caballero Sanchez:** None. **E. Morelos:** None. **P. Reyes:** None. **A. Medina-Rivera:** None. **J. Esquivias:** None. **S. Alcauter:** None. **M.E. Rentería:** None. **A. Ruiz-Conteraras:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.03/X3

Topic: C.03. Parkinson's Disease

Support: Udall Center of Excellence in Parkinson's Disease Research: NIH P50 NS123109
MnDRIVE DBS Core

Title: The relationship of pallidal local field potentials to ankle rigidity in Parkinson's disease

Authors: *E. VAFAEI[1], S. L. AMUNDSEN HUFFMASTER[1], M. VACA[1], Y. CHOI[1], J. CHUNG[1], L. WINTER[1], P. TUITE[1], M. C. PARK[2], S. E. COOPER[1], J. L. VITEK, MD, PHD[1], C. D. MACKINNON[1];
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Abstract: Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is an effective therapy for appendicular rigidity in people with Parkinson's disease (PD), yet the mechanisms contributing to reduced rigidity are poorly understood. Moreover, little is known about the pathophysiology of leg rigidity in PD and it has been hypothesized that its mechanisms may be different from the arm. The goal of this ongoing project is to investigate the relationship between quantitative measures of ankle rigidity and local field potentials (LFPs) recorded from DBS electrodes in the globus pallidus of people with PD. We hypothesized that DBS would decrease ankle rigidity and that the changes in rigidity would correlate with measures of LFP power in the GP. People with a Medtronic Percept GPi-DBS system were recruited for a single study visit in the OFF-medication state. LFPs were recorded during DBS wash-out (turning off stimulation) and wash-in (turning on stimulation) conditions. Data was collected at 15-minute intervals (0-75 min). Baseline recordings were obtained in both the DBS-on (prior to wash-out) and DBS-off (prior to wash-in) conditions. Rigidity was tested on the ankle contralateral to the DBS electrode, with and without an activation maneuver (finger tapping contralateral to the ankle). A custom servo-controlled manipulandum passively rotated the ankle about the dorsiflexion-plantarflexion axis in a sinusoidal motion from 5 to -25 deg at 1.5 Hz. Primary outcome measures were peak negative power, angular impulse, and negative work, as well as LFP beta power. All measures of rigidity were significantly higher in the activation-maneuver condition than in the passive condition during the wash-out trials ($P<0.001$), but not during wash-in. Rigidity tended to increase and decrease in an inverse exponential function during wash-out and wash-in, respectively. Overall, ON DBS rigidity was significantly lower than OFF DBS. The mean and standard deviation of low beta power (13-20 Hz) were significantly lower during ON vs. OFF DBS. However, there was no significant correlation between low beta power and ankle rigidity. These findings demonstrate that while DBS improves rigidity and suppresses low beta-band power in the GPi, beta-band power in LFPs and ankle rigidity do not appear to be related.

Disclosures: E. Vafaei: None. **S.L. Amundsen Huffmaster:** None. **M. Vaca:** None. **Y. Choi:** None. **J. Chung:** None. **L. Winter:** None. **P. Tuite:** None. **M.C. Park:** None. **S.E. Cooper:** None. **J.L. Vitek, MD, PhD:** None. **C.D. MacKinnon:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.04/X4

Topic: C.03. Parkinson's Disease

Support: University of Delaware Department of Kinesiology and Applied Physiology Dissertation Grant
NIH R03 NS146865
Unidel Foundation Distinguished Graduate Scholar Fellowship

Title: The impact of dual-tasking on bimanual motor performance and brain activity in older adults with and without Parkinson's disease

Authors: *A. BOWER[1], N. GETCHELL[1], E. OFORI[3], M. COHEN[1], J. MARTELLO[4], R. G. BURCIU[2];
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder resulting in motor and cognitive impairment. Some aspects of dual-tasking in upper limb tasks remain unexplored but are important for independent living. This study investigates the effect of dual-tasking on a bimanual force control task and underlying brain activity in individuals with and without PD. Fifteen healthy older adults (OA) and nine people with PD performed ten trials of a bimanual isometric force control task at 15% and 30% of their maximum voluntary contraction (MVC) in 20s blocks interspersed with 20s of rest. This was performed as a stand-alone task and with a concurrent selective attention task in the dual-task condition. Prefrontal cortex (PFC) activity was measured as ΔHbO with functional near-infrared spectroscopy. Both groups had greater force variability at 30%MVC, and PD was more variable than OA in the dual-tasking conditions. A dual-task effect in force error was found for PD in the 30%MVC condition and for OA in the 15%MVC condition. While no significant differences in ΔHbO were observed between groups, patterns suggesting reduced PFC activity in PD were present. In the PD group, negative correlations were found between the dual-task cost for error at 30%MVC and multiple measures of cognitive performance, whereas no associations were found with motor symptom severity. The descriptive patterns in ΔHbO suggested reduced PFC activation in PD during dual-task performance, which may reflect altered prefrontal engagement during bimanual control tasks. Additionally, cognitive characteristics in individuals with PD may serve as predictors of dual-task interference.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Program #/Poster #: PSTR264.05/X5

Topic: C.03. Parkinson's Disease

Support: NIMH Grant R01 MH127200
Robert and Janice McNair Foundation

Title: Altered salience network connectivity with non-motor neuropsychiatric symptoms in Parkinson's disease

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Abstract: Apathy, anxiety, and depression are common neuropsychiatric (NPS), non-motor symptoms in Parkinson's disease (PD) and may result from dysfunction in motivational and salience networks involving the striatum (Str), dorsal anterior cingulate cortex (dACC), and anterior insular cortex (AIC). We investigated whether structural connectivity among the regions of interest (ROIs) was associated with the severity of NPS symptoms in PD. We hypothesized that NPS symptoms would be associated with alterations in white matter integrity along pathways involving the ROIs. Fifty-eight participants with PD completed a psychological assessment battery (Dimensional Apathy Scale, General Anxiety Disorder-7, Geriatric Depression Scale). Disease severity was measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Participants underwent a 3T MRI to acquire a T1 image (voxel size=0.8mm isotropic) and diffusion-weighted images (DWI; voxel size=2.2mm isotropic). DWIs were preprocessed to generate fractional anisotropy (FA) maps and registered to MNI space. Using the MICCAI atlas, our ROIs were identified on subject-specific T1 image and warped to DWI space. Then, anatomy constrained tractography was performed to generate subject-specific tract masks between the ROIs. These masks were registered to MNI space; group consensus masks were generated using a 25% threshold for voxelwise analyses. FSL randomise with threshold-free cluster enhancement, family-wise error correction, and 500 permutations was used to examine associations between voxelwise FA and NPS symptoms controlling for age, disease duration, levodopa equivalent daily dose, and UPDRS scores. Severe apathy was associated with increased FA in inferior segments where the left dACC-Str and AIC-Str tracts converge (t=4.6, $pFWE$=0.03). Within these focal segments, the positive apathy-FA relationship was significantly different from the negative depression-FA relationship (t=3.4, $pFWE$=0.03). Trend-level positive associations between FA and depression were observed in anterior segments of the right dACC-Str tracts (t=4.0, corrected p=0.05) and the external capsule segments of the left AIC-Str tracts (t=3.2, corrected p=0.05). In PD, greater apathy was associated with increased diffusion anisotropy in the white matter segments where dACC and AIC projections to the striatum converge, potentially a key white matter hub for the salience network. These findings suggest that reduced complexity of local fiber architecture in this salience network crossing-fiber region contributes to high FA and apathy and highlighting partially distinct neural substrates for apathy and depression in PD.

Disclosures: H. Suzuki: None. **H.L. Combs:** None. **N. Vanegas-Arroyave:** None. **S.R. Heilbronner:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Program #/Poster #: PSTR264.06/X6

Topic: C.03. Parkinson's Disease

Support: National Research Foundation of Korea (NRF) (No. 2020R1C1C1013160)

Title: Gray matter alterations and neurochemical correlates in isolated REM sleep behavior disorder

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Abstract: Purpose: Multiple neurotransmitter systems are implicated in the pathophysiology of isolated rapid eye movement sleep behavior disorder (iRBD) and its progression to α-synucleinopathy. This study aimed to identify baseline gray matter (GM) alterations in patients with iRBD compared with healthy controls and to examine their spatial correspondence with known neurotransmitter distributions. We further characterized GM patterns associated with future phenoconversion and their neurochemical context.
Methods: A total of 109 patients with iRBD who completed at least one follow-up evaluation and 24 age- and sex-matched healthy controls underwent structural magnetic resonance imaging. Gray matter volume (GMV) alterations were assessed using the CAT12 toolbox. Spatial correlations between group-level GMV difference maps and neurotransmitter atlases were evaluated using the JuSpace toolbox.
Results: At baseline, patients with iRBD showed reduced GMV in the right cerebellar cortex and vermis, along with increased GMV in the left putamen and pallidum. These GMV alterations demonstrated significant spatial correspondence with dopaminergic receptor and transporter maps, including dopamine D2 receptors and the dopamine transporter (DAT). Among patients with iRBD, those who subsequently phenoconverted exhibited lower baseline GMV in the right medial orbital gyrus compared with non-converters. This pattern showed significant spatial correlations with serotonergic (5-HT2A), glutamatergic (mGluR5), GABAergic (GABAa), and dopaminergic (FDOPA) neurotransmitter ma.
Conclusion: Patients with iRBD exhibit distinct patterns of GMV alteration that spatially align with dopaminergic neurotransmitter distributions, while phenoconversion is associated with GM changes corresponding to multiple neurotransmitter systems. These findings provide a neurochemical framework for structural brain vulnerability in iRBD and may offer potential targets for monitoring or modulating disease progression.

Disclosures: J. Byun: None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: NWO HMM 18954
Maastricht University, FHML stimulation fund

Title: Altered Thalamic Connectivity of a Bladder-Related PAG Subdivision in Parkinson's Disease

Authors: J. HALEWIJN[1], A. BELCHER[2], A. KNOPS[3], G. A. VAN KOEVERINGE[4], M. KUIJF[5], M. DE RIJK[1], ***J. VAN DEN HURK**[6];
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Abstract: Lower urinary tract symptoms are among the most common non-motor manifestations of Parkinson's disease (PD), yet the neural mechanisms underlying these symptoms remain poorly understood. The periaqueductal gray (PAG) and Barrington's nucleus are key components of the supraspinal circuitry involved in bladder sensation and micturition control. We investigated whether functional connectivity of these regions is altered in PD.
Resting-state 7T fMRI data from 30 patients with PD and 30 healthy controls, originating from the TrackPD-study were included. Seed regions included three PAG subdivisions (based on independent group level mapping of the human PAG in vivo) roughly corresponding to a rostral, mid and caudal PAG, and Barrington's nucleus. Seed-to-region connectivity was calculated using the AAL3 atlas supplemented with subcortical and brainstem regions. Correlation coefficients were Fisher z-transformed prior to analysis. Group differences were assessed using non-parametric statistics. To evaluate systems-level alterations, connectivity between each seed region and thalamic, limbic, and cerebellar groups was quantified by averaging connectivity across all regions within each group. Resulting network scores were compared between groups and corrected for multiple comparisons using FDR-correction across all seed-network combinations.
Exploratory ROI-based analyses identified multiple connectivity differences involving thalamic, cerebellar, limbic, and basal ganglia regions. The most prominent pattern involved caudal PAG, which demonstrated increased connectivity with both left and right lateral posterior thalamic nuclei in PD patients. To evaluate whether these convergent findings reflected broader systems-level alterations, connectivity was averaged across anatomically related regions into network-level metrics. This confirmed significantly increased connectivity between caudal PAG and a thalamic network in PD ($p = 0.0007$, FDR-corrected $p = 0.008$). No other network-level effects survived correction for multiple comparisons.
These findings suggest that Parkinson's disease is associated with altered connectivity of a PAG subdivision identified during bladder sensation processing, with the strongest effects involving bilateral thalamic relay regions implicated in sensory integration. The convergence of whole-brain and network-level analyses points to altered supraspinal processing of bladder-related information in PD and identifies PAG-thalamic circuitry as a potential neural substrate contributing to lower urinary tract dysfunction.

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Poster

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Program #/Poster #: PSTR264.08/X8

Topic: C.03. Parkinson's Disease

Support: National Natural Sciences Foundation of China 81600982
National Natural Sciences Foundation of China 2541160282

Title: Higherorder Tactile Motion Deficits Reveal Sensorimotor Network Reorganization in Akinetic rigid Parkinson's disease

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Abstract: Parkinson's disease (PD) is associated with somatosensory dysfunction, yet tactile-motion integration deficits remain elusive. In this study, we combined psychophysical assessment of tactile-motion perception with resting-state functional MRI (rs-fMRI) to investigate how alterations in sensorimotor network organization relate to higher-order tactile-motion deficits in akinetic-rigid dominant PD (PD_{AR}). Forty-six participants, including 25 PD_{AR} patients (57.12 ± 1.44 yrs; 13 females) and 21 age- and sex-matched healthy controls (HCs; 53.90 ± 1.08 yrs; 12 females), underwent clinical evaluation and rs-fMRI scanning. A subset (15 PD_{AR} and 15 HCs) completed a tactile-motion task assessing directional bias and speed sensitivity. Region of interest (ROI)-to-ROI functional connectivity (FC) analyses were performed within a customized 26-node sensorimotor and cortico-basal ganglia-thalamo-cortical (CBGTC) network. Compared with HCs, PD_{AR} patients exhibited significantly altered tactile-motion perception during Welch's *t*-tests, characterized by greater systematic directional bias [PD_{AR} = -14.66°±2.70°, HC = -2.86°±4.92°; t(21.72) =2.11, $p = 0.047$)], a shifted tuning phase in nonsystematic bias [t(17.76) = 2.53, $p = 0.021$], and reduced speed sensitivity indicated by a flattened psychophysical slope [t(26.10) = 3.99, $p < 0.001$], reflecting impaired discrimination of intermediate-to-high tactile speeds. At the network level, omnibus comparisons revealed significant FC alterations across primary motor and somatosensory ROIs, including Area 4 and Area 3b [all p-FDR<0.01, F(2,43) > 6.5]. Post-hoc *t*-tests revealed widespread hypoconnectivity within cortical sensorimotor circuits (e.g., Area3b L-Area 1 R: $t(44) = 3.43$, p-FDR = 0.016). Conversely, hyperconnectivity emerged between subcortical and sensorimotor regions, including Area 5 R-internal globus pallidus (GPi) L [t(44) = −3.57, p-FDR=0.022] and Area 4 L-Thalamus L pathways [$t(44) = -3.22$, p-FDR=0.015]. Together, these findings identify a behavioral-neural phenotype in PD_{AR}, where reduced cortical somatosensory integration together with increased subcortical-cortical coupling was associated with higher-order tactile-motion deficits. These results suggest that large-scale sensorimotor network dysfunction contributes to tactile-motion deficits in PD_{AR}. These findings highlight the role of distributed sensorimotor networks in PD-related somatosensory dysfunction.

Disclosures: B. Qu: None. **C. Gao:** None. **H. Lai:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Program #/Poster #: PSTR264.09/X9

Topic: C.03. Parkinson's Disease

Support: R21NS128391

Title: Cortical $alpha_4beta_2$ nicotinic acetylcholine receptor density correlates with DLPFC theta oscillations and cognitive function in Parkinson's disease

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Abstract: Introduction: Parkinson's Disease (PD) can cause non-motor symptoms such as cognitive disfunction associated with reduction in $alpha_4beta_2$ nicotinic acetylcholine receptor ($alpha_4beta_2$-nAChR) binding in the dorsolateral prefrontal cortex (DLPFC). Theta (4-9 Hz) brain oscillations in the DLPFC are implicated in cognitive control and gating of neural activity, while beta (13-30 Hz) oscillations are associated with PD motor symptoms. The relationship between cholinergic signaling and theta oscillations in local field potential recordings is unclear. We seek to clarify the mechanism for cognitive dysfunction in PD by exploring the interrelationship between cognitive performance, DLFPC theta oscillations, and $alpha_4beta_2$-nAChR density.
Methods: 5 PD patients underwent baseline cognitive testing to assess attention, executive function, language, working memory, verbal memory, visuospatial memory, and visuospatial perception. During awake surgery, a grid of electrocorticography (ECoG) electrodes over the left DLPFC captured beta and theta oscillations whose average power was estimated. 2 out of 5 subjects completed an intraoperative n-back cognitive task. Additionally, the DLPFC was identified on MRI using the Human Connectome Project atlas, and ^{18}F-XTRA PET imaging assessed the total volume of distribution (V_T) of $alpha_4beta_2$-nAChR in regions under each of the 21 rows of the ECoG grid. Within subjects, row-wise theta power was compared to V_T, and theta power between rest and the n-back task was compared where applicable. Across all subjects, the average theta and beta power were compared with preoperative cognitive domain composite T-scores.
Results: In 4 out of 5 subjects, across DLPFC regions, V_T and theta power were positively correlated. For both subjects who completed the cognitive task, theta power was lower during the task compared to pre-task period. In all subjects, there was a trend toward a positive correlation between resting theta power in the DLPFC and attention and working memory domains, while visuospatial perception tended to inversely correlate with theta power. There were no trends between mean beta oscillation power and cognitive function.

Conclusion: Resting theta oscillation power appears to positively associate with alpha$_4$beta$_2$-nAChR density and baseline cognitive function, suggesting that the presence of theta-range signals driven by cholinergic signaling is beneficial towards the preservation of cognitive function in PD. However, theta power seems to decrease during a cognitive task, suggesting that the ability to acutely decrease theta activity is also important for cognitive function.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Topic: C.03. Parkinson's Disease

Support: National Natural Science Foundation of China 82101547
National Natural Science Foundation of China 82471495

Title: Target-specific transcranial temporal interference stimulation modulates somato-cognitive action network-subcortical connectivity in Parkinson's disease

Authors: *X. GUAN[1], A. LI[2], S. BAI[3], Y. LU[1], C. ZHANG[1];
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Abstract: Parkinson's disease (PD) has been conceptualized as a disorder of somato-cognitive action network (SCAN)-subcortical coupling, but whether noninvasive stimulation of deep motor targets engages this circuit is unknown. We conducted a secondary, mechanism-focused analysis of a randomized, double-blind, sham-controlled, three-condition crossover study in 21 adults with mild-to-moderate PD (66.9±7.0 years; 11 male) tested in the medication-OFF state. Each participant received 20 min of unilateral transcranial temporal interference stimulation (tTIS) targeting the subthalamic nucleus (STN), globus pallidus internus (GPi), or sham, in randomized order. The temporal interference envelope was 130 Hz; the stimulation hemisphere was contralateral to the more affected body side. Motor severity and resting-state fMRI were acquired before and after each session. Linear mixed-effects models estimated changes in Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) and Fisher z-transformed functional connectivity between a cortical SCAN template and six PD-relevant subcortical seeds. Both active conditions improved motor severity relative to sham: STN-tTIS reduced MDS-UPDRS III by 4.57 points more than sham (95% CI, -7.38 to -1.76; P=0.002), and GPi-tTIS reduced it by 2.80 points more than sham (95% CI, -5.56 to -0.04; P=0.047). STN-tTIS produced the clearest bradykinesia improvement (difference vs sham, -2.91; P=0.002). Despite convergent clinical benefit, the targets produced opposite SCAN-subcortical

connectivity effects. Relative to sham, STN-tTIS increased SCAN-subcortical connectivity (difference in change, 0.084; P=0.009), whereas GPi-tTIS decreased it (difference in change, -0.136; $P=5.75\times10^{-5}$). Seed- and graph-level analyses suggested distributed reconfiguration: STN-tTIS selectively strengthened cortico-subthalamic action-control connectivity, whereas GPi-tTIS broadly dampened an over-coupled pallidal output graph. These data show that single-session tTIS can noninvasively access deep Parkinsonian motor circuitry and that STN and GPi stimulation converge on acute motor benefit through distinct SCAN-subcortical network operations.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Program #/Poster #: PSTR264.11/X11

Topic: C.03. Parkinson’s Disease

Title: Predicting monopolar local field potential power from bipolar recordings in deep brain stimulation

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Abstract: Deep brain stimulation (DBS) is an established therapy for movement disorders such as Parkinson's disease (PD), essential tremor, and dystonia. Modern DBS devices can record local field potentials (LFPs) to guide DBS therapy. LFPs from implanted DBS devices are typically limited to bipolar configurations to suppress common-mode noise and reduce large artifacts that can obscure physiological activity. However, bipolar recordings can also attenuate local physiological signals. Establishing a method to convert bipolar to monopolar power could yield more spatially precise estimates of LFP activity, thereby more effectively guiding DBS. Herein, we develop a model to estimate monopolar power from bipolar recordings.
This retrospective study analyzed data from 64 leads across 50 patients with PD undergoing STN (11) or GPi (53) DBS implantation. Intraoperatively, LFPs were recorded from all contacts (C0, C1, C2, and C3) and filtered. Bipolar montages were generated for each combination. Power spectral density (PSD) was calculated from each monopolar and bipolar signal, averaged over canonical frequency bands, and processed as log PSD. A common set of 3 bipolar configurations was selected across all recordings by minimizing the Condition Number (CN) to maximize model stability. Monopolar and bipolar powers were related using robust ordinary least squares regression. Observations were randomly partitioned into training and validation sets.
Sixty four leads yielded 640 observations across 50 patients with PD. The configuration group with the lowest CN (7.45) was {C03, C12, C23}. The models demonstrated adjusted R2s of

0.9015, 0.9055, 0.8853, and 0.8764, and RMSEs (dB) of 3.2663, 3.2801, 3.5815, and 3.7035, respectively, when predicting C0, C1, C2, and C3 using the training data (N = 500; all $p < 0.0001$). Performance was verified across STN, GPi, hemisphere-specific, and combined cohorts. This study demonstrates that monopolar LFP power can be accurately estimated from bipolar power using a linear regression model with strong generalizability across targets and validation sets. This approach offers a hardware-agnostic solution to spatially disambiguate signals and better inform DBS programming and adaptive stimulation in chronically implanted devices. A pretrained companion script is available.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Topic: C.03. Parkinson’s Disease

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R01 NS081118
R01 NS113746
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1R01 NS124814

Title: Motor evoked potentials as markers of internal capsule current spread during deep brain stimulation for Parkinson's Disease

Authors: *L. WINTER[1], E. E. LECY[2], C. LU[2], T. PALNITKAR[2], J. CHANDRASEKARAN[2], Y. SEDDIGHI[2], R. PATRIAT[2], M. D. JOHNSON[2], N. HAREL[2], C. D. MACKINNON[2], S. E. COOPER[2];
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Abstract: Deep brain stimulation (DBS) of the globus pallidus internus (GPi) and subthalamic nucleus (STN) is highly effective for managing cardinal motor symptoms in Parkinson’s disease. However, unintended spread of activation to corticospinal and corticobulbar fibers in the adjacent internal capsule can cause involuntary muscle contractions. While intraoperative threshold testing is common and certain recruitment patterns are widely assumed, systematic

empirical data detailing multi-muscle motor responses simultaneously across both surgical targets remains limited. We characterized upper and lower limb motor evoked potentials (MEPs) produced by DBS to determine how stimulation location and orientation affect responses. Low-frequency DBS was delivered in the globus pallidus internus (GPi, 17 hemispheres) and subthalamic nucleus (STN, 8 hemispheres). MEPs were identified by stimulus-triggered averaging of surface electromyography (sEMG) from nine contralateral upper and lower extremity muscles. Stimulation amplitudes were limited to 1-5 mA to mimic therapeutic limits. Area under the curve (AUC) and onset latencies were calculated.No significant differences were observed in MEP onset latencies or magnitudes (AUC) between GPi and STN targets across any muscle group ($p > 0.14$), suggesting that descending pathway recruitment characteristics are comparable between targets. Regionally, upper limb MEP magnitudes were significantly larger than lower limb responses ($p < 0.001$), perhaps reflecting closer somatotopic proximity of the leads to upper extremity capsular fibers. A strict proximal-to-distal gradient was established: distal muscles showed higher incidence and magnitude than proximal muscles ($p < 0.001$), with response rates steadily declining from distal ring 1 to proximal ring 4 ($p < 0.003$). Further, a consistent recruitment hierarchy was observed: the thenar muscles were the most sensitive responders. Thenar MEP absence was associated with a 96% probability of MEP absence in all other muscles. Directional contact analysis at 3 mA revealed strong selectivity ($\rho = 0.88$), with postero-medial segments yielding 5.6 fold larger MEPs than antero-lateral segments ($p < 0.05$). This spatial resolution deteriorated at higher stimulation amplitudes as current spread widened.This study establishes a predictable hierarchy of MEPs during deep brain stimulation, identifying distal upper limb muscles, specifically the thenar, as the most sensitive indicators of corticospinal activation. These findings provide a robust physiological framework for quantifying and avoiding stimulation-induced side effects in patients with Parkinson’s disease.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.13/X13

Topic: C.03. Parkinson’s Disease

Support: JSPS KAKENHI 23K19933
JSPS KAKENHI 23K19984
Keio University, Center for Parkinson’s Disease Research

Title: Clinical Efficacy of EEG Beta-Burst Neurofeedback Training in Patients with Parkinson's Disease: A Preliminary Experiment

Authors: *Y. HAMANO[1], S. OKUSA[2,5], H. SAEGUSA[3,5], S. IWAMA[4], M. SEKI[2,5], J. USHIBA[4];
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Abstract: Pathological beta-band (13-35 Hz) bursts within the sensorimotor cortex are linked to motor deficits in Parkinson's disease (PD). While neurofeedback training (NFT) shows promise, its empirical efficacy in driving meaningful behavioral improvements in movement precision and altering motor execution dynamics requires validation. This study evaluated the behavioral impact of real-time EEG-based NFT on finger-tapping performance in patients with PD. Five patients with PD (N=5) participated in the experiment. The intervention consisted of real-time EEG-NFT where patients performed kinesthetic motor imagery of thumb-index finger tapping targeting individual sensorimotor beta burst metrics. Resting-state activity and actual physical tapping execution were assessed immediately before and after the training session. Quantitative kinematics and electrophysiological burst characteristics were compared. Linear Mixed Model (LMM) analysis on behavioral metrics revealed a significant Time-per-tap*Session (Pre vs. Post) interaction(β=-1.49, t=-3.02, p=0.013). Post-NFT sessions demonstrated modifications in kinematic profiles, with the temporal trajectory of physical finger movements becoming more consistent across the duration of each tap compared to pre-NFT baselines. These data suggest an immediate, acute modulation of movement execution following the intervention. Our preliminary findings demonstrate that EEG-targeted burst NFT using motor imagery can drive meaningful behavioral improvements in actual movement dynamics in PD. These results highlight the therapeutic potential of NFT as a non-invasive, behaviorally-focused intervention, supporting further investigation within ongoing patient cohorts.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

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MnDRIVE DBS Core
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Title: Effects of pallidal deep-brain stimulation in people with Parkinson's disease while performing upper-limb rapid-alternating movements.

Authors: ***M. A. VACA**[1], S. L. AMUNDSEN HUFFMASTER[1], J. CHUNG[1], Y. CHOI[2], M. N. PETRUCCI[1], M. E. LINN-EVANS[2], C. MAUPIN[1], E. E. LECY[1], S. E. COOPER[1], M. C. PARK[3], P. TUITE[1], J. L. VITEK, MD, PHD[4], C. D. MACKINNON[1];
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Abstract: People with Parkinson's disease (PD) frequently experience significant movement impairments when performing rapid alternating movements (RAMs), particularly at higher tempos (e.g., > 2 Hz). Performance impairments may include slowing, a sequence effect (progressive decrease in amplitude), freezing (movement interruption), or festination (low amplitude, high frequency movements). Although deep brain stimulation (DBS) is an effective intervention for some aspects of bradykinesia, little is known about the effects of pallidal DBS (GP-DBS) on RAMs. Here, we used a wrist RAMs task to characterize the effect of GP-DBS on features of RAMs impairment. We hypothesized that ON GP-DBS would improve the amplitude and timing of wrist RAMs compared to OFF GP-DBS.Twelve people with PD (5 females, ages: 63-75 years old, time since diagnosis = 9.3± 3.3 years) and GP-DBS (8 bilateral) completed a wrist pronation-supination RAMs task in the ON and OFF GP-DBS states (tested on separate days). Each test was performed OFF PD medications (12+ hours). Repetitive pronation-supination movements of the forearm were assessed using an instrumented manipulandum. Movements were visually guided (target movement amplitude: ±15 deg) and acoustically paced (target rates randomly alternated between epochs of 1 and 2 Hz, with 4 epochs per 60s trial). Six trials were completed with each arm contralateral to an implanted DBS device. Primary outcome measures were angular displacement (root mean square, RMS, of the angular position), speed (RMS of the derivative of angle), and delta frequency (the absolute value of the difference between the peak movement frequency and the target frequency) for the 2 Hz epochs. Linear mixed effects models (Rstudio) investigated the effect of DBS with arm as a random factor. Significance was set to $p < 0.05$. All three measures showed significant main effects of GP-DBS setting, with ON DBS increasing angle (df=457, t=6.36, p<0.001) and velocity (df=457, t=7.33, p<0.001) and decreasing delta frequency (df=457, t=-5.64, p<0.001).An increase in movement amplitude and speed, along with a delta frequency trending towards 0, suggests an improvement towards matching the target amplitude and frequency when DBS was ON. These finding provide evidence that GP-DBS improves the performance of higher rate (2 Hz) RAMs.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.15/X15

Topic:

Support: 1K23NS117735
UH3-NS130202

Title: Intracortical neural mechanisms of cognitive control in patients with Parkinsons disease and essential tremor

Authors: *A. MYSORE[1], M. T. HOLLAND[1], V. DEL BENE[2], J. THUM[3], R. T. KNIGHT[4], H. C. WALKER[5], N. BENTLEY[1];
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Abstract: Introduction: Cognitive control involves processing sensory information from the environment and identifying relevant cues to precisely govern actions. Motor control occurs in an anticipatory (proactive) or late-corrective (reactive) manner. Patients with Parkinson's disease (PD) often exhibit impaired cognitive control and altered scalp potentials compared to healthy controls. However, the spatiotemporal dynamics of these EEG signals remain debated. Here, we investigated the neural basis of cognitive control in patients with movement disorders using temporary subdural cortical recordings during deep-brain stimulation (DBS) surgery. **Methods:** Twelve patients (five with PD and seven with essential tremor, ET) performed an AX-version of the continuous performance task (AX-CPT) during DBS surgery. The task evaluates cognitive control by presenting a conditioning cue followed by a probe event requiring context-dependent responses. In the proactive context, the patient must anticipate a response based on the conditioning cue. The reactive context requires the patient to override the cue conditioning and wait for the probe to execute a response. To observe neural interactions between brain areas associated with cognitive control, two six-contact electrocorticography (ECoG) strips were temporarily placed along the cortex during routine clinical DBS surgery: one anteriorly over the dorsolateral prefrontal cortex (DLPFC) and one posteriorly over the primary motor cortex, ipsilateral to the DBS implant. **Results:** Four PD patients and two ET patients had higher error rates in the proactive context. Additionally, ECoG contacts in the left rostral DLPFC displayed sustained gamma power (60-200 Hz) during proactive control (200 ms after cue onset until response) but transient peak activity during reactive control (for 250 ms before response). Moreover, the ET patients displayed stronger sustained low-frequency activity (2-8 Hz) in the proactive context in bilateral rostral DLPFC during the anticipatory response interval (100 ms after cue onset until response) compared to PD patients. **Conclusion:** Rostral DLPFC shows differential activation in low frequencies and the high frequency broadband in proactive versus reactive control based on different movement disorders. Ongoing analyses are evaluating the spatiotemporal dynamics of these responses by recording site, brain hemisphere, and disease. Better understanding these dynamics could expand fundamental knowledge on cognitive control and guide future neuromodulation therapies.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Program #/Poster #: PSTR264.16/X16

Topic: C.03. Parkinson's Disease

Support: NIH Grant UG3/UH3 NS130202

Title: Deep brain stimulation local evoked neural potentials differ among globus pallidus interna, globus pallidus externa, and subthalamic nucleus

Authors: *S. A. BRINKERHOFF[1], A. MYSORE[2], H. COWART[3], A. NAKHMANI[5], N. BENTLEY[4], M. T. HOLLAND[4], J. THUM[4], H. C. WALKER[1];
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Abstract: Introduction: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) is an established treatment for Parkinson disease (PD). DBS of these structures evokes local neural responses, including ERNA a stimulus-locked oscillatory field potential that exhibits short-term facilitation. Although the globus pallidus externa (GPe) is not a canonical stimulation target, whether GPe DBS elicits ERNA is unknown. Methods: 8 patients with PD underwent awake unilateral dual-target DBS surgery, receiving an 8-contact directional lead in the STN followed by another lead in the GPi. During implantation, the surgeon advanced the leads at 2-mm intervals en route to each target, during which we delivered monopolar stimulation from the ventral directional contacts. Along the pallidal trajectory, this anatomic span included stimulation and recording within the GPe. Biphasic stimuli were delivered at 3 mA and 60 μsec pulse width across single and paired pulses with interstimulus ranging from 0.8 to 15.3 ms. Recordings were rereferenced to a bipolar montage, detrended, filtered using Savitzky-Golay filters, and analyzed using the Coastline Burst Index (CBI) - accumulated voltage - from 3 to 20 ms after the test pulse. We contrasted the short-term facilitation of response latency and magnitude (CBI) across the three regions (STN, GPi, GPe) by paired pulse interval. Results: Stimulation within the STN and GPi elicited ERNA with characteristic short-term facilitation. In contrast, GPe stimulation evoked a morphologically distinct field potential response in all 8 patients that instead displayed paired-pulse depression. Conclusions: In 8 patients with PD, paired pulse stimulation in the GPe elicited a local field potential response distinct from STN and GPi ERNA that displayed short-term depression rather than facilitation. These findings expand the map of stimulus-evoked physiology across the human basal ganglia and may help identify functionally distinct subregions during DBS targeting.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR264.17/X17

Topic:

Support: UG3NS130202

Title: Evoked potential magnitude scales with deep-brain stimulation amplitude in the subthalamic nucleus in Parkinson's disease

Authors: *H. COWART[1], S. A. BRINKERHOFF[2], A. NAKHMANI[4], M. T. HOLLAND[3], N. BENTLEY[3], J. THUM[5], H. C. WALKER[6];
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Abstract: Introduction: Deep brain stimulation (DBS) is an established treatment for the motor symptoms of Parkinson's disease (PD). Subthalamic nucleus (STN) elicits multiple local neural responses, including a tapering sinusoidal oscillation called evoked resonant neural activity (ERNA). STN DBS contacts that display larger ERNA magnitude are associated with effective therapy, suggesting it could serve as a clinically relevant biomarker for circuit engagement. Here, we sought to better characterize how STN DBS amplitude alters ERNA across the therapeutic window - a clinically defined amplitude range that defines sub-therapeutic, therapeutic, and adverse DBS parameters for a given stimulation site. Methods: Five patients with PD underwent awake unilateral STN DBS surgery with an 8-contact directional lead. During lead implant, we delivered monopolar stimuli below, within, and above the therapeutic window (60 μsec pulse width, 80 stimuli per condition). The therapeutic window was established intraoperatively. We recorded responses from the unused adjacent contacts, binned the signals into 27 ms windows from -2 to +25 ms after stimulus onset, and constructed bipolar montages between horizontal adjacent directional contacts. We then compared ERNA magnitude as a function of DBS amplitude relative to the therapeutic window. Results: ERNA magnitude increased non-linearly near the therapeutic window floor and began to plateau around the therapeutic window ceiling. After testing different models, quadratic or logarithmic models best fit the magnitude of the response to stimulation amplitude in all participants. Conclusions: In five patients with PD, ERNA magnitude scaled non-linearly with DBS amplitude, with the largest increases at the therapeutic window floor and an asymptote near the therapeutic window ceiling. These findings have potential implications for the relationship between ERNA magnitude and clinical outcomes

and suggest that ERNA could inform tailored neuromodulation strategies for both open- and closed-loop DBS for Parkinson's disease and other movement disorders.

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Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.18/X18

Topic: C.03. Parkinson's Disease

Title: Burst frequency-dependent modulation of evoked resonant neural activity by DBS

Authors: *A. VARGHESE[1], S. BRINKERHOFF[2], A. NAKHMANI[4], J. THUM[5], M. T. HOLLAND[3], N. BENTLEY[3], H. C. WALKER[6];
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Abstract: Deep brain stimulation (DBS) is a neuromodulation therapy that electrically stimulates key basal ganglia structures to improve abnormal movements in patients with Parkinson's disease and related disorders. Symptom reduction depends on many variables such electrode placement, stimulation configuration, and stimulus amplitude and frequency. Conventionally, DBS at >100 Hz is required to improve tremor, but the mechanistic basis for this phenomenon is unclear. ERNA, or the evoked resonant neural activity, is a local neural response found approximately 3-4 ms after electric stimulation in the subthalamic nucleus and globus pallidus interna. Its amplitude is larger in STN than in GPi but shows paired pulse facilitation at both sites. How these responses evolve in the context of bursts and/or continuous stimulation is unclear. Here we sought to contrast changes in ERNA in response to 200 ms stimulus bursts at effective and ineffective stimulation frequencies (e.g. 30 versus 130 Hz). Biphasic stimuli were delivered at a therapeutic amplitude determined by a neurologist performing brain mapping for electrode targeting with pulse width of 60 μsec. DBS bursts at therapeutic frequencies initially increase the amplitude and shorten the latency of ERNA, however this facilitation often diminishes by the conclusion of the 200 ms burst. In contrast, bursts at an ineffective frequency (30 Hz) do not significantly alter ERNA amplitude or latency. Our findings suggest that DBS synchronizes activity in the basal ganglia circuitry and that ERNA short-term facilitation may relate to its therapeutic effects. Future studies require similar recordings over longer time intervals to better understand the potential relevance of ERNA as a biomarker to guide both open- and closed-loop approaches to DBS therapy.

Disclosures: A. Varghese: None. **S. Brinkerhoff:** A. Employment/Salary (full or part-time):; UAB. **A. Nakhmani:** None. **J. Thum:** None. **M.T. Holland:** None. **N. Bentley:** None. **H.C. Walker:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

Location: WCC Halls A-C

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BRAIN Initiative UM1MH136462

Title: A sensitive orange fluorescent calcium ion indicator for imaging neural activity

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Abstract:



Genetically encoded calcium indicators (GECIs) enable fluorescence-based monitoring of neuronal activity with high spatial and temporal resolution. However, the highest-performance GECIs are predominantly green or red fluorescent proteins, limiting opportunities for multiplexed imaging and efficient excitation using widely available fixed-wavelength femtosecond lasers operating above 1000 nm.
To address this gap, we engineered OCaMP, an orange fluorescent GECI derived from O-GECO1 through structure-guided mutagenesis to improve calcium affinity while preserving the favorable photophysical properties of the mOrange2 scaffold. OCaMP exhibits enhanced calcium affinity, improved two-photon excitation cross-section, increased photostability, and larger fluorescence responses compared with O-GECO1. We characterized OCaMP in cultured neurons, zebrafish, and mouse cortex, where it enabled robust detection of neuronal activity with high sensitivity and signal-to-noise ratio.
Across preparations, OCaMP outperformed the red GECIs jRCaMP1a and jRGECO1a in responsiveness, photostability, and signal fidelity. The orange spectral properties of OCaMP support efficient excitation with cost-effective industrial lasers operating at wavelengths above 1000 nm and facilitate multiplexed imaging alongside existing green and red indicators.
Together, these results establish OCaMP as a high-performance orange GECI that expands the available spectral palette for calcium imaging and provides a practical tool for high-fidelity measurements of neural activity across diverse experimental systems.

Disclosures: A. Aggarwal: None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR264.20/X20

Topic:

Support: NIH BRAIN Initiative Grant UH3 NS130202

Title: Subthalamic nucleus stimulation elicits phase-locked pallidal neuronal firing aligned to evoked resonant neural activity

Authors: *E. DUNBAR[1], S. A. BRINKERHOFF[2], A. NAKHMANI[4], A. MYSORE[3], M. T. HOLLAND[1], J. THUM[5], N. BENTLEY[1], H. C. WALKER[6];
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Abstract: Introduction: Deep brain stimulation (DBS), a valuable therapy for Parkinson's disease, elicits an oscillatory field potential termed evoked resonant neural activity (ERNA) during local stimulation in either the subthalamic nucleus (STN) or the globus pallidus interna (GPi). These two regions are the primary drivers of the indirect pathway, where the STN sends excitatory glutamatergic projections to the GPi to modulate movement. While local ERNA in the STN and GPi is well known, it is unclear if stimulation of STN would elicit ERNA in the pallidum. The mechanistic basis of this oscillatory field potential is unknown as well. **Materials & Methods:** Six patients with PD underwent awake DBS surgery with unilateral implants in both the STN and pallidum. We delivered single and paired electrical stimulus pulses from the subthalamic nucleus macroelectrode and recorded spikes and microscopic local field potentials in the ipsilateral pallidum. Pulses were biphasic with 3 mA amplitude, 80-40-80 μs phases, interstimulus intervals ranging from 0.45 to 7.7 ms, and ≥50 ms between conditions. We parsed spikes into clusters for manual unit consolidation and generated stimulus-locked spike patterns and histograms for overlay onto the ERNA waveform from the subthalamic pallidal field potentials. **Results:** STN stimulation yields ERNA in both the internal and external segment of the pallidum. Spikes align with ERNA oscillations in both pallidal segments, and discharge probability changes based on paired pulse interval. **Conclusion:** Single and paired pulses delivered to the subthalamic nucleus elicited time-locked action potentials and ERNA in the ipsilateral pallidum. These findings indicate that ERNA is a circuit-level phenomenon within the indirect pathway and suggest that its mechanistic basis at least partially arises from neuronal spike timing. Collectively, our results suggest that therapeutic deep brain stimulation synchronizes neural activity within basal ganglia circuits.

Disclosures: E. Dunbar: None. **S.A. Brinkerhoff:** None. **A. Nakhmani:** None. **A. Mysore:** None. **M.T. Holland:** None. **J. Thum:** None. **N. Bentley:** None. **H.C. Walker:** None.

Poster

PSTR264: Parkinson's Disease: Circuit Mechanisms in Humans

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Topic: C.03. Parkinson's Disease

Support: R01-NS124563, NIH NINDS
T32-Neurodegeneration
UAB RMS

Title: State-Dependent Beta Dynamics in the Human Subthalamic Nucleus During Voluntary Movement and Passive Sensory Stimulation

Authors: *A. KEY[1], J. JADAPALLI[2], N. BENTLEY[3], H. C. WALKER[4];
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Abstract: The subthalamic nucleus (STN) is a key basal ganglia structure involved in motor control; however, STN also serves neglected roles in sensory integration. Oscillatory activity in the beta frequency range (13-30 Hz) within the STN is associated with motor impairment in Parkinson's disease and is modulated during voluntary movement. Motor cortex local field potentials demonstrate differential beta-band modulation during active and passive movements, motivating examination of whether analogous distinctions are present within the STN. Determining whether STN oscillatory activity differs between volitional movement and passive proprioceptive input may provide insight into how basal ganglia-thalamocortical circuits represent motor versus sensory aspects of behavior.
We examined STN local field potential recordings collected from PD patients intraoperatively during three behavioral conditions: rest, active hand movement, and passive limb movement (proprioceptive stimulation). Time-frequency analyses using continuous wavelet transform (CWT) will quantify changes in beta (13-30 Hz) and broadband (30-200 Hz) power and their temporal dynamics across conditions. Condition-dependent differences in oscillatory modulation will be assessed to characterize how STN activity varies with motor output versus sensory-driven input. Preliminary analyses of STN recordings indicate condition-dependent modulation of beta-band activity across active movement, and passive vibratory stimulation of the wrist. STN oscillatory activity exhibits state-dependent modulation across active and passive movements compared to rest. By distinguishing how oscillatory dynamics differ across these conditions, we hope to clarify how STN contributes to sensorimotor integration within the distributed motor circuit. These findings may improve mechanistic models of basal ganglia function and inform future approaches to adaptive neuromodulation in movement disorders.

Disclosures: A. Key: None. **N. Bentley:** None. **H.C. Walker:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

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Program #/Poster #: PSTR265.01/X22

Topic: C.03. Parkinson's Disease

Support: NINDS UH3NS128150
Robert and Ruth Halperin Foundation
John E. Cahill Family Foundation

Title: Effect of combined subthalamic nucleus and intermittent nucleus basalis of Meynart deep brain stimulation for cognitive impairment in Parkinson's disease.

Authors: *M. PAPWORTH BURREL[1], P. ACHARYYA[2], C. CASSELTON[3], A. ABAY[2], K. CHIMNI[1], K. B. WILKINS[4], R. CROCKETT[11], V. BUCH[5], J. M. HENDERSON[6], D. T. BLAKE[12], G. K. DEUTSCH[7], B. REID[8], M. M. ZEINEH[9], H. BRONTE-STEWART[10]; [1]Stanford Univ., Palo Alto, CA; [3]Neurol. and Neurolog. Sci., [2]Stanford Univ., Stanford, CA; [4]Neurol., [5]Neurosurg., Stanford Univ., Palo Alto, CA; [6]Dept Neurosurgy, R 227, Stanford Univ., Stanford, CA; [7]Stanford Univ., San Clemente, CA; [8]Stereotactic and Functional Neurosurg., Stanford Univ., Palo Alto, CA; [9]Radiology, Stanford Univ., Stanford, CA; [10]Neurol. and Neurolog. Sci., Stanford Univ., Palo Alto, CA; [11]Oxford Univ., Oxford, United Kingdom; [12]Neurosci. and Regenerative Med., Med. Col. of Georgia at Augusta Univ., Augusta, GA

Abstract: Parkinson's disease (PD) manifests with both motor and non-motor symptoms including cognitive impairment. Subthalamic nucleus (STN). Deep Brain Stimulation (DBS) successfully addresses the motor symptoms but does not improve cognition. The Nucleus Basalis of Meynert (NBM) is a major hub for the cortical cholinergic network and is known to degenerate even in early-stage PD. The NBM is a large flat structure and difficult to target with one DBS lead. However it channels its outflow into two major fibre bundles, the lateral bundle supplying the majority of the cortex. Intermittent DBS of the anterior NBM increases working memory and cortical acetylcholine response in animal models providing rationale for potential efficacy in PD cognitive impairment. In this study we targeted either the NBM lateral efferent bundle or the preclinical anterior NBM target and tested the safety and efficacy of bilateral continuous STN (130 Hz, 60µs) and intermittent NBM (1hr/day intermittent 60Hz, 100µs: 10sec ON/40sec OFF stimulation) people with PD and mild cognitive impairment. Four lead patterned neurostimulation was made possible using investigational Boston Scientific Chronos Software. Cognitive and motor tasks were completed at baseline and every 6 months with the primary outcome at 12 months. Cognitive and motor tasks were completed at baseline and every 6 months with the primary outcome at 12 months. We have currently enrolled 7 people, 5 implanted (3 with the anterior target and 2 with the lateral bundle target). No adverse events occurred during or after the DBS leads implantation. Leads were accurately placed that image guided algorithmic programming (Illumina) generated volumes of tissue activation (VTAs) that optimized overlap with the target and avoidance of surrounding structures. Motor symptoms improved in all participants as expected; monthly check-ins and a continued assessment of capacity to consent showed that bilateral STN+NBM DBS is both safe and tolerable for those with PD with cognitive impairment. Preliminary results of cognitive testing after 6 months of

bilateral STN+NBM DBS demonstrated improvement in the primary outcome Parkinson's Disease Cognitive Rating Scale (PD-CRS) in 4/4 participants so far tested. One participant, who has completed their 12 month visit, continued to show improvement in their PD-CRS score from their initial baseline scores. These preliminary results show that bilateral STN+NBM DBS is safe, well tolerated and shows promise for potentially improving the cognitive motor syndrome in people with PD and cognitive impairment.

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Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.02/X23

Topic: C.03. Parkinson's Disease

Support: This work has been supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT)(RS-2026-25483609). This work has been supported by the National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT)(RS-2022-NR070207).

Title: Multimodal exercise shifts Parkinson's disease-associated gut microbiota toward a healthy reference profile: an exploratory randomized trial analysis

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Abstract: Background: Parkinson's disease (PD) is associated with gut dysbiosis, including depletion of short-chain fatty acid (SCFA)-associated taxa and enrichment of taxa linked to mucosal or inflammatory pathways. Whether Meridian Activation Remedy System for Parkinson's Disease (MARS-PD) neurorehabilitation modulates this dysbiosis remains unclear. Methods: Fecal samples were collected at baseline and week 8 from 65 PD participants (37 MARS-PD, 28 control) in a single-center randomized trial (n=88 randomized). 16S rRNA V3-V4 amplicon sequencing was performed using Illumina MiSeq. An age-matched external healthy reference cohort (HC; n=617, PRJEB33905) contextualized PD-associated alterations. Alpha-diversity and beta-diversity distances (Bray-Curtis, unweighted UniFrac) were assessed. Differential taxa were identified by LEfSe (LDA>=2.0) and ANCOM-BC (FDR q<0.1). MCID response was defined by MDS-UPDRS Part I (>2.64 points) and Part III (>3.25 points) improvement.

Results: Compared with HC, PD participants showed reduced richness (observed features: 81.1±36.7 vs. 111.6±29.0, $p=4.1\times10^{-10}$; Chao1: 106.8±55.4 vs. 173.8±57.8, $p=9.9\times10^{-15}$) and diversity (Shannon: 4.99±0.83 vs. 5.47±0.65, $p=2.6\times10^{-6}$), with distinct beta-diversity separation (PERMANOVA $p<0.001$). PD microbiota showed depletion of putative SCFA-associated taxa, including Coprococcus, Dorea, Roseburia, Prevotella, and Lachnospiraceae_uncultured, with enrichment of Enterococcus and Akkermansia. After 8-week MARS-PD, Dorea, Prevotella, Lachnospiraceae_uncultured, and [Eubacterium]_ventriosum_group shifted toward the HC reference distribution. Alpha- and beta-diversity did not differ between MCID responders and non-responders. Lachnospiraceae_NK4A136_group and Bacteroides showed nominal associations with Part III and Part I response, respectively ($p=0.02$ each), but no taxa survived FDR correction.
Conclusions: In this exploratory microbiome analysis nested within a randomized trial, MARS-PD was associated with partial shifts of PD-depleted SCFA-associated taxa toward a healthy reference profile. Microbiome-clinical response associations were hypothesis-generating only. These findings support the gut-brain axis as a candidate pathway of exercise-based neurorehabilitation in PD.

Disclosures: M.S. Park: None. **H. Yoo:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.03/Web Only

Topic: C.03. Parkinson’s Disease

Title: Multidisciplinary Design Optimization for Deep Brain Stimulation, the Confluence of Neuroscience and Rocket Science

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Abstract: Deep brain stimulation offers breakthrough treatment of Parkinson’s disease. However, the convergence to an optimal parameter configuration can present a daunting challenge. Multidisciplinary design optimization, which derives from the domain of rocket science, is applied in a first of its kind application to ascertain an optimal parameter configuration. Inherent to multidisciplinary design optimization is the use of contrarian relationships to define a dependent variable, for which an optimal is determined based on the associated independent variables. For example, maximal stimulation power can elicit minimal tremor, but this condition implies overuse of critical deep brain stimulation battery available charge. Minimal stimulation power promotes extended battery lifetime at the expense of amplified tremor. In the context of multidisciplinary design optimization a dependent variable defined as a function of combined deep brain stimulation power, which is a function of amplitude setting, and hand tremor power, which is a function of the measured inertial sensor

signal acquired from a conformal wearable, derives a topology defined as an effective power, which is a function of a primary independent variable based on deep brain stimulation amplitude. An assortment of deep brain stimulation amplitude settings for a subject with Parkinson's disease are applied. The application of multidisciplinary design optimization for deep brain stimulation treatment of Parkinson's disease achieves an optimal effective power corresponding with an optimal amplitude setting.

Disclosures: R.C. LeMoyne: None. **T.J. Mastroianni:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.04/X24

Topic: C.03. Parkinson's Disease

Title: Motor complications associated with continuous dopaminergic stimulation or intermittent levodopa in patients with early-stage Parkinson's disease: a retrospective database study

Authors: *R. TANG[1], F. GAO[3], X. LIN[1], Y. HE[1], J. WANG[2], C. MAO[3], **C.-F. LIU**[3]; [1]Organon, Shanghai, China; [2]Organon, Point Cook, Australia; [3]The Second Affiliated Hosp. of Soochow Univ., Suzhou, China

Abstract: Continuous dopaminergic stimulation (CDS) may delay motor complications (MCs) associated with intermittent levodopa for Parkinson's disease (PD). This retrospective database study compared the onset of MCs between CDS and immediate-release (IR) levodopa treatments in early PD. We retrieved datasets from two longitudinal observational studies, the Parkinson's Progression Markers Initiative (PPMI) and the Fox Insight Data Exploration Network (FOXDEN). Analyzed participants were early PD adults assessed as Hoehn & Yahr stage 1-2, baseline MDS-UPDRS Part III score ≤24, or PD <3 years. All participants received oral levodopa monotherapy, either controlled- or extended-release (CDS) or IR. The primary endpoint was the time from levodopa initiation to the first MC, defined as dyskinesia or off-time (MDS-UPDRS Part IV confirmed or patient-reported). The Kaplan-Meier method estimated the median MC-free duration [months (95%CI)] and compared MC occurrence between the two groups using the log-rank test. The primary analysis combined datasets and included 1,774 patients (CDS: 257; IR: 1517). The mean age (years) at diagnosis was similar across treatment groups (PPMI: 62.0-63.2; FOXDEN: 65.3-66.6), with median treatment exposure of 19.5-36.0 months. The median MC-free duration did not differ between the two groups [CDS: 27.6 (24.0-34.2); IR: 27.6 (26.0-29.0)]. The median dyskinesia- and off-time-free durations were also similar [52.8 (43.0-63.0) vs. 53.0 (49.0-58.0); 30.0 (25.0-33.6) vs. 28.8 (27.6-30.0)]. The CDS had numerically lower cumulative incidences of MC, dyskinesia, and off-time compared with IR (64.6% vs. 72.5%; 26.2% vs. 39.2%; 61.8% vs. 70.4%; all p = NS). In PPMI (1077; CDS: 163; IR: 914), median MC-free and off-time-free durations were significantly lower in the CDS group (17.0 vs. 26.0; 23.0 vs. 29.0); In FOXDEN (697; CDS: 94; IR: 603), a greater median off-time-

free duration was observed in the CDS group (36.0 vs. 28.0). In secondary analyses, CDS did not increase the risk of moderate-to-severe off-time [OR: 1.13 (0.42-3.01); p=0.81), adjusted for age at diagnosis, gender, and weight in multivariate logistic model. The QoL analysis did not show significant differences between the two groups. In summary, CDS-based levodopa was associated with numerically lower MC incidence but did not clinically delay MC onset compared with IR. The database-specific analysis yielded conflicting findings for off-time-free durations, whereas dyskinesia onset was late and comparable across treatments. This retrospective study had limitations in outcome assessment and an imbalance in participants, warranting future randomized controlled trials.

Disclosures: R. Tang: None. **F. Gao:** None. **X. Lin:** None. **Y. He:** None. **J. Wang:** None. **C. Mao:** None. **C. Liu:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.05/X25

Topic: C.03. Parkinson’s Disease

Support: FAPESP/Brazil #2024/01132-2
FAPESP/Brazil #2025/02493-1

Title: Transcranial photobiomodulation changes postural control functioning of people with Parkinson’s disease: Preliminary results

Authors: *J. A. BARELA[1], P. GUTIERREZ[1], B. FURLANETTO[1], P. DE FREITAS BICHARA[1], D. ORCIOLI-SILVA[2];
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Abstract: Recent evidence suggests that transcranial photobiomodulation (tPBM) may contribute to reducing motor symptoms in Parkinson’s disease (PD). This technique involves the non-invasive application of light to specific regions of the cerebral cortex, potentially promoting neuroprotective effects and modulating neuronal activity. However, despite promising findings, the evidence remains inconclusive, particularly regarding the effects of tPBM on postural control in individuals with PD. Therefore, the present study aimed to evaluate the effects of tPBM on balance in individuals with PD. Nine participants diagnosed with PD took part in this study. The experimental protocol consisted of 20 visits. Postural control assessments occurred during the first and last visits (off-medication) while tPBM sessions were administered from the second to the nineteenth visit (on-medication), 3 times a week for 12 minutes each. Postural control was assessed using a force platform when participants stood upright, eyes open, 3 trials lasting 30 seconds each. Results showed that ellipse area, mean sway amplitude and velocity increased after the tPBM interventions. Despite the small sample size, these preliminary results show

changes in postural control, leading to larger magnitude and higher sway velocity. Although the increase in magnitude and velocity in body sway needs to be further investigated, the tPBM might be promising as a rehabilitation strategy for people with PD.

Disclosures: J.A. Barela: None. **P. Gutierrez:** None. **B. Furlanetto:** None. **P. de Freitas Bichara:** None. **D. Orcioli-Silva:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.06/X26

Topic: C.03. Parkinson’s Disease

Support: NIH Grant UH3NS140730

Title: Toward Automated Programming for Adaptive Deep Brain Stimulation in Parkinson’s Disease: In Silico and Patient-based Validation of a Parameter Optimization Pipeline

Authors: *J. YAO[1,2,4], G. ESHED[2], S. LIU[2], M. ZHU[2], C. SHI[5], L. LI[6], P. A. STARR[1,3], S. LITTLE[2,3];
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Abstract: Conventional constant deep brain stimulation (cDBS) is a standard treatment for Parkinson’s disease (PD), but residual motor symptoms can occur due to its failure to adapt to the changing needs of the brain. Adaptive DBS (aDBS) involves stimulation amplitude modulation based on biomarkers of neural and clinical states, and has been shown to offer superior symptom control compared to cDBS. However, aDBS significantly expands the existing parameter space and requires considerable expertise for programming and fine-tuning, potentially limiting its broader clinical implementation.
Here we introduce an offline optimization pipeline that simultaneously evaluates multiple adaptive control parameters in a commercially available bidirectional neurostimulator, using clinical data routinely available in outpatient practice as input. Using recorded in-clinic and at-home basal ganglia activity from 15 PD patients, we designed and validated multiple submodules that predict the final adaptive control for any aDBS setting and computed a clinically-relevant metric ("aDBS fit") quantifying how closely the delivered adaptive stimulation tracks the patient's reported symptom state. The modules were then combined with an optimizer algorithm which iteratively explores and suggests new candidate dual-threshold adaptive settings. Offline end-to-end pipeline performance was then evaluated in a subset of 7 patients (11 hemispheres with complete data) who had residual motor fluctuations on cDBS.

In offline evaluation, the optimization pipeline produced individualized aDBS parameter recommendations with high predicted aDBS fit (mean = 87.5% ± 10.0% across the top 1% of settings; maximum = 97.9% ± 2.8%). Constrained optimization of thresholds alone yielded lower maximum performance than full multi-parameter optimization ($p = 0.042$, two-sided Wilcoxon signed rank test). Optimized thresholds in constrained optimization deviated systematically from device-recommended percentile values. Based on these results, we have demonstrated an integrated offline optimization pipeline that can generate personalized aDBS parameter recommendations using outpatient clinical data. Prospective testing with in-clinic and at-home evaluation of pipeline-suggested adaptive settings is currently underway.

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Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.07/X27

Topic: C.03. Parkinson’s Disease

Title: Modulation of Cortico-Subcortical Network Dynamics During Forced and Voluntary Exercise in Parkinson's Disease

Authors: *V. BERKI[1], S. DAVIDSON[3], A. BAZYK[3], M. MILLER KOOP[4], A. ROSENFELDT[3], J. L. ALBERTS[2];
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Abstract: People with Parkinson's disease (PD) experience motor and cognitive impairments that may improve following aerobic exercise, yet the real-time cortico-subcortical dynamics underlying these effects remain poorly understood. This preliminary study examined minute-by-minute cortical and subthalamic nucleus (STN) beta-band modulation during forced exercise (FE) and voluntary exercise (VE) in individuals with PD.
Six individuals with PD (4 males, 2 females; mean age 68.7 years; mean disease duration since diagnosis 7.1 years) implanted with sensing-enabled deep brain stimulation systems participated. Testing was performed in the OFF-medication and OFF-stimulation states. Chronic STN local field potentials were synchronized with 64-channel mobile EEG during continuous FE and VE paradigms. Event-Related Desynchronization/Synchronization (ERDS) was calculated in the beta band for predefined EEG regions and STN beta-max channels. STN activity was summarized using the right max beta channel, left max beta channel, and bilateral average of both max beta channels. Minute-by-minute ERDS trajectories were evaluated during active exercise and post-exercise rest relative to pre-exercise baseline.
Preliminary descriptive analyses showed exercise-related beta modulation across cortical and STN recordings. During active exercise, STN beta activity shifted toward desynchronization

relative to baseline, with comparable patterns observed in the right STN, left STN, and bilateral beta-max STN average. In contrast, EEG activity showed increased beta synchronization during exercise across frontal and motor cortical regions, indicating distributed cortical engagement during cycling. VE produced more pronounced beta modulation than FE, while FE showed comparatively smaller or less sustained minute-by-minute changes. During post-exercise rest, STN beta desynchronization attenuated toward baseline and cortical beta synchronization diminished after movement cessation, suggesting a transient residual network response rather than a sustained post-exercise shift.
These preliminary findings suggest that synchronized STN LFP and high-density EEG recordings can capture dynamic cortico-subcortical beta modulation during exercise in PD. Minute-by-minute ERDS analysis may help differentiate the neural effects of FE and VE and support future work aimed at optimizing exercise-based rehabilitation and neuromodulation strategies.

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Poster

PSTR265: Parkinson's Disease: Clinical Trials

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.08/X28

Topic: C.03. Parkinson’s Disease

Support: The Maggie E. Neumann Health Sciences Research Fund

Title: Acute Effects of High-Definition tDCS on Motor-Related fMRI Activity and Postural Control in Parkinson's Disease

Authors: *M. QUATTRUCCI[1], A. BOWER[1], R. G. BURCIU[2], J. MARTELLO[3];
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Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder marked by the depletion of dopamine. The resulting motor impairments can manifest as challenges with walking and balance, which often respond insufficiently to dopaminergic medication. This pilot study examines the acute effects of high-definition transcranial direct current stimulation (HD-tDCS) applied to the medial sensorimotor cortex (M1S1) on motor-related functional MRI activity and postural control in individuals with and without PD. Seven participants (2 PD, 5 older adult controls) completed 20-minute active-stimulation and sham sessions in a randomized order. The stimulation was delivered to M1S1 inside the MRI scanner using a 4×1 HD-tDCS montage at 1.67 mA. An ankle dorsiflexion force task was used pre- and post-session to assess lower-limb fMRI activity. Balance was assessed outside the scanner before and after each HD-tDCS-MRI session using a lumbar-mounted inertial measurement unit (IMU) during several 30-s

trials with eyes open and closed on firm and soft surfaces. The PD patients were tested following ~12 h washout from PD medication. In the two PD participants, there appears to be an increase in M1S1 activity after the stimulation intervention, but not during the sham session. The sway area was reduced in PD patients following stimulation, particularly under challenging sensory conditions, whereas older adults showed no change. Sham treatments produced no notable effects in any group. These preliminary findings suggest that HD-tDCS targeting the medial M1S1 may modulate both cortical activity and postural control in PD; however, additional participants will be needed to confirm these effects.

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Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.09/X29

Topic: C.03. Parkinson's Disease

Support: R01NS129115-02

Title: Validation of the Comprehensive Augmented Reality Testing Platform for the Quantification of Upper Extremity Reciprocal Pointing in Parkinson's Disease

Authors: *A. BAZYK[1], R. KAYA[3], E. ZIMMERMAN[1], C. WALTZ[2], A. ROSENFELDT[1], M. MILLER KOOP[4], J. L. ALBERTS[4];
[2]Biomed. Engin., [1]Cleveland Clin. Fndn., Cleveland, OH; [4]Biomed. Engin., [3]Cleveland Clin., Cleveland, OH

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease that impacts the quantity and quality of movement required for independent living and successful completion of activities of daily living. The precise assessment and tracking of PD motor performance isn't achieved using traditional clinical scales. The most widely used clinical scale in PD, the Movement Disorders Society-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III), is a subjective rating scale that lacks reliability and sensitivity. Conversely, motion capture systems are capable of accurate and objective quantification of motor symptoms but are cost prohibitive and lack portability. The Comprehensive Augmented Reality Testing (CART) platform was designed to fill the gap for an objective motor evaluation that is cost-effective and portable. By leveraging the depth and infrared camera on a commercial augmented reality (AR) headset along with commercial pose estimation software, three-dimensional biomechanics of the hand can be evaluated. Individuals self-administer assessment of their hand movements with both instructions and data collection coming from the self-worn AR headset. Gold-standard motion capture markers were placed on the hands and recorded concurrently. A total of 82 individuals with PD and 36 age-matched healthy controls completed a reciprocal pointing task, once with each hand. Participants were instructed to move their hand back and forth quickly and

smoothly between two digital targets ~26cm apart. It was hypothesized that the CART derived outcomes would: 1.) demonstrate criterion validity, with the CART outcomes being statistically equivalent (within 5%) of the gold-standard motion capture and 2.) differentiate performance between people with PD and healthy controls. Outcomes characterizing movement speed, amplitude, smoothness and hesitations were statistically equivalent within 5% between CART and gold-standard motion capture. Movement speed, smoothness, hesitations and variability as measured by CART differentiated individuals with PD and healthy controls. The CART platform demonstrates criterion and known-groups validity for a reciprocal pointing task. The CART platform provides objective, accurate and quantitative measures of PD motor performance, using a single portable device conducive to clinical integration.

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Poster

PSTR265: Parkinson's Disease: Clinical Trials

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.10/X30

Topic: C.03. Parkinson’s Disease

Support: NIA Grant RO1AG081356
BPTPS Grant P30CA177558

Title: Autologous Peripheral Nerve Grafts Adopt Sustained Repair-State Phenotype after Transplantation into the Substantia Nigra or Nucleus Basalis of Meynert of Participants with Parkinson's Disease

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[1]Neurosci., [2]Neurosurg., Univ. of Kentucky, Lexington, KY

Abstract: Neurodegenerative disorders share a common feature in progressive loss of vulnerable neuronal populations within aging tissue environments. Dopaminergic (DA) neurons of the substantia nigra (SN) and cholinergic neurons of the nucleus basalis of Meynert (NBM) degenerate across Parkinson's disease (PD), Parkinson's disease dementia, dementia with Lewy bodies, and Alzheimer's disease, contributing to motor and cognitive impairment. Current therapies do not halt this loss. Strategies to support surviving neurons through transplantation have been explored for decades, yet immunological rejection, reactive astrogliosis, and inhibitory CNS extracellular matrix (ECM) have collectively prevented sustained graft survival in the human brain. An NIA-funded clinical program has stereotactically implanted autologous peripheral nerve tissue (PNT) grafts derived from sural nerve fascicles into the SN or NBM of over 90 participants with PD. The autologous origin eliminates immunosuppression requirements. Postmortem donations from this cohort permit investigation of grafts surviving as

long as 10 years, the longest characterized survival of PNT transplants in the human brain. Histological analysis demonstrates long-term graft survival with maintained vasculature, peripheral nervous system (PNS) architecture, and cellular viability across participants, with consistent collagen type I alpha 1 (COL1A1) ECM boundaries and minimal astrocytic infiltration. Spatial transcriptomic analysis of SN grafts identifies a coherent PNS signature concordant across participants and tissue sections, including repair-state Schwann cell markers (p75NTR, SCN7A, CDH19, GFRA1), endoneurial fibroblast and ECM remodeling transcripts, and developmental transcription factors that coordinate structural plasticity and repair in peripheral nerves (NR2F2, EBF2, MEOX2). Canonical myelinating Schwann cell markers (MAG, MOG, PLP1, MYRF) are absent, supporting a chronic non-myelinating phenotype rather than homeostatic mature nerve state. Multiplexed immunofluorescence confirms protein-level Schwann cell, fibroblast, and ECM marker expression and direct astrocytic apposition at the graft-host interface. Proteomic findings from transected sural nerves demonstrate elevated GDNF, BDNF, and c-JUN, markers of repair-state phenotype whose transcriptional regulators are enriched in transplanted PNT grafts. These findings provide evidence that autologous PNT grafts sustain a repair-state PNS environment within the degenerating human CNS that could support vulnerable neuronal populations in the nuclei most affected by neurodegenerative disease.

Disclosures: A. Marlonsson: None. **J.E. Quintero:** None. **C.G. van Horne:** None. **G.A. Gerhardt:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

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Program #/Poster #: PSTR265.11/X31

Topic: C.03. Parkinson’s Disease

Support: Delaware Bioscience Center CAT grant KAAP422149
University of Delaware college of Health sciences Big Ideas grant HNSC412171

Title: Exploring the effects of Transcranial Photobiomodulation (tPBM) for Parkinsons Disease Motor and Cognitive Symptoms

Authors: *S. PENUELA[1], P. P. GUTIERREZ[5], J. J. JEKA[2], T. BUCKLEY[3], J. A. BARELA[5], R. G. BURCIU[4];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNc) and accumulation of Lewy bodies. This dysregulation contributes to the motor and non-motor symptoms of PD, including slowness of movement, rest tremor, rigidity, postural instability, and cognitive decline. PD is

highlighted as a heterogeneous condition, contributing to notable variability in symptom and treatment response among individuals. To date, most treatments target symptom management, such as dopamine replacement therapies, but fail to address the underlying neuronal vulnerability and metabolic stress that characterizes PD. As a result, there is a need for more effective therapies that target the metabolic stress and cellular degradation common across PD phenotypes. Our pilot study explores Transcranial PhotoBioModulation (tPBM), a non-invasive therapy that uses near-infrared light to stimulate brain tissue; increasing cellular energy, cerebral blood flow, and reducing cell death. Given the frontal cortex's role in executive function and its connection to the basal ganglia, we investigated whether tPBM delivered to the frontal cortex can improve motor and cognitive symptoms in PD. tPBM was delivered 3 times/week for 6 weeks (810nm wavelength, irradiance -500mW/cm2, 12 min/session), with pre- and post-assessments of cognitive and motor function performed in the off-medication state (12h washout). Motor symptom severity was assessed clinically using MDS-UPDRS-III alongside a wearable motion sensor system (kinesiaOne). To date, 33 participants (age: 71.2 ± 6.70, 11F, 22M) have completed the intervention at multisite locations (USA and Brazil), with 18 receiving active and 15 receiving sham treatment. Preliminary results suggest that the active treatment group showed greater improvements (lower scores) for KinesiaOne total and upper-extremity scores compared to the sham group. Total MDS-UPDRS-III scores for the active group also showed clinically significant reductions in motor impairment compared to the sham group. The intervention is ongoing to solidify these findings. If effective, tPBM could serve as a powerful additive therapy for PD, potentially improving symptoms and enhancing quality of life

Disclosures: S. Penuela: 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 Delaware Grant #KAAP422149. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NeuroThera. **P.P. Gutierrez:** None. **J.J. Jeka:** None. **T. Buckley:** None. **J.A. Barela:** None. **R.G. Burciu:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.12/X32

Topic: C.03. Parkinson's Disease

Title: 7T MRI for DBS Placement in Parkinson's Disease

Authors: *V. S. SICA, A. FRANKINI, G. R. ZANGHI;
Rowan-Virtua Sch. of Osteo. Med., Stratford, NJ

Abstract: Parkinson's disease (PD) is characterized as a progressive neurodegenerative disease that often presents with features of tremor, rigidity, bradykinesia, and postural instability (Michou et al., 2017). The pathogenesis of PD involves dopaminergic neuron loss in the

substantia nigra pars compacta, accumulation of α-synuclein/Lewy bodies, and degeneration of important regions for noradrenergic, parasympathetic, serotonergic,cholinergic, and dopaminergic signaling (Lees et al., 2009). Deep Brain Stimulation (DBS) has been used to improve motor symptoms by modulating abnormal basal ganglia circuitry, most commonly targeting the subthalamic nucleus (STN) or globus pallidus internus (GPi) (Deuschl et al., 2006). Preoperative MRI, most commonly performed at conventional field strengths such as 1.5T or 3T, is routinely used to guide DBS target identification, trajectory planning, and lead placement. However, clinical outcomes following DBS depend heavily on accurate lead placement, target visualization, and trajectory planning. (Weaver FM, et al., 2012).
One way to improve DBS lead placement is through using Ultra High Field (UHF) 7 Tesla MRI. Shifting from 3T to UHF linearly increases the SNR, allowing higher spatial resolution and decreased noise (Cramer et al., 2024). Furthermore, UHF enhances susceptibility-based tissue contrast (Cramer et al., 2024). Taken together, this enables more precise identification of deep brain structures relevant to DBS planning (Cramer et al., 2024). In PD, this may be particularly relevant for visualising the dorsolateral STN, a functionally important subregion associated with motor benefit after STN DBS. In a study by Verlaat et al. (2024), 7T T2-weighted MRI was used to identify the dorsolateral STN for DBS electrode placement. The study found increased visual alignment of electrode trajectories and longer recording per channel, suggesting UHF MRI use improves anatomical targeting and streamlines intraoperative mapping.
Despite the benefits of UHF MRIs, they still have technical and practical limitations. Signal Loss near air and bony structures can occur due to increased susceptibility maps, while shorter RF wavelengths and increased RF heterogeneity may produce non-uniform images (Cramer et al., 2024). Therefore, while 7T MRI offers a promising strategy for improving DBS planning in PD, further prospective studies are needed to determine whether improved anatomical visualisation translates into superior long-term motor outcomes, lower stimulation requirements, fewer stimulation-related adverse effects, and more individualised DBS programming strategies.

Disclosures: V.S. Sica: None. **A. Frankini:** None. **G.R. Zanghi:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.13/Y1

Topic: C.03. Parkinson’s Disease

Support: Fondazione Pezzoli per la Malattia di Parkinson – ETS
Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) Project-ID 424778381 - TRR 295

Title: Characterization of sleep-related subthalamic dynamics and wearable sleep staging performance in Parkinson's disease

Authors: *L. CAFFI[1,2], S. CASCINO[3], I. U. ISAIAS[1,2,3], C. PALMISANO[1,2];
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Abstract: Sleep disturbances are common in Parkinson's disease (PD). Although subthalamic nucleus deep brain stimulation (STN-DBS) may improve sleep, its effects on sleep stages remain incompletely understood. Sensing-enabled DBS systems provide chronic recordings of STN local field potentials (LFP), which could serve as biomarkers for sleep-aware adaptive DBS (aDBS), but their validation requires polysomnography (PSG). Wearable devices may offer a practical alternative for long-term sleep monitoring, although their performance in PD remains unclear. We combined PSG, STN-LFP recordings, and wearable monitoring to characterize sleep-related neural signatures and assess wearable-based sleep staging in PD. We collected data from 4 patients (male; mean [range] age: 53 [42-61] yrs; disease duration: 16 [11-20] yrs) treated with beta-based aDBS (linear proportional algorithm; AlphaDBS). Participants underwent overnight PSG with synchronized LFP recordings and ECG monitoring (RootiRx, 3 patients). Sleep stages were scored by an expert neurologist. Neural recordings consisted of power spectral density estimates in the 5-34 Hz range with 10-min resolution. Normalized power was computed in the alpha (8-11 Hz), low-beta (12-20 Hz), and high-beta (21-30 Hz) bands. Wearable sleep staging was evaluated against PSG using accuracy and Cohen's kappa (K). Sleep efficiency was 79.3 [70-88]%, with wake after sleep onset of 116.3 [57-200] min. Rapid eye movement (REM) sleep and non-REM (NREM) stages N1, N2, and N3 accounted for 21.2 [14.3-28.7]%, 17.9 [13.5-21.8]%, 44.9 [35.7-52.2]%, and 16.0 [10.7-20.5]% of total sleep time, respectively. Compared with wakefulness, NREM sleep was characterized by lower low-beta and high-beta power and higher alpha power, whereas REM sleep showed intermediate spectral profiles. The wearable achieved two-stage (sleep/wake) classification accuracy of 86.6 [81.6-90.7]% with moderate agreement (K, 0.5 [0.4-0.6]). Four-stage classification accuracy was highest for wakefulness (86.6 [81.6-90.7]%), followed by REM sleep (83.5 [77.8-87.2]%), deep sleep (83.2 [79.3-87]%), and light sleep (67.5 [61.5-69.3]%), yielding overall fair agreement (K, 0.37 [0.3-0.4]). Patients exhibited fragmented sleep with reduced N3 sleep and sleep-stage-dependent STN-LFP modulation. Wearables adequately detected sleep/wake states but showed limited accuracy for four-stage sleep classification. These findings further highlight the need for further technological improvements and validation in larger patient cohorts before reliable wearable-based sleep-stage monitoring can be achieved.

Disclosures: L. Caffi: None. **S. Cascino:** None. **I.U. Isaias:** 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.; Newronika S.p.A.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Newronika S.p.A.. F. Consulting Fees (e.g., advisory boards); Newronika S.p.A. **C. Palmisano:** 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.; Medtronic.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.14/Y2

Topic: C.03. Parkinson's Disease

Title: World's First Phase 2 Interim Results of NouvNeu001, a Chemically Derived Dopaminergic Progenitor Cell Therapy, for the Treatment of Advanced Parkinson's Disease

Authors: H. CHEN[1], C. NIU[2], N. XIONG[3], N. XIONG[4], H. SHANG[5], M. CAI[6], X. REN[6], R. YAN[6], ***J. WEI**[6];
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder due to loss of nigral dopaminergic neurons, leading to a broad spectrum of motor and non-motor symptoms. There is currently no therapy capable of reversing the progression of PD, and cell replacement strategies represents a potential disease-modifying therapeutic approach. This study investigates safety, tolerability, and efficacy of a chemically induced iPSC-derived human dopaminergic progenitor cell therapy, NouvNeu001, in advanced Parkinson's disease. Previous Phase 1 results demonstrated favorable safety and efficacy, and we now report the 6 months interim follow-up data from the ongoing Phase 2 trial. The Phase 2 study enrolled 30 patients aged between 50 and 75 years. All patients underwent bilateral transplantation of NouvNeu001 into the putamen with a single trajectory per hemisphere. The NouvNeu001 transplantation was safe and well-tolerated in all 30 patients. At the 6 months interim follow-up (N=17), MDS-UPDRS Part III motor mean scores changed from baseline 58.47±2.54 points to 6 month follow-up 41.65±3.44 points in the "OFF" state, and changed from baseline 30.09±3.63 points to 6 month follow-up 22.18±3.19 points in the "ON" state. Adjusted PD diary good ON time increased from baseline 7.92±0.55 hours to 6 month follow-up 9.54±0.87 hours. The mean PDQ-39 score changed from baseline 48.77±3.84 points to 6 month follow-up 40.29±4.17 points. In summary, preliminary data from ongoing phase 2 trial showed sustained improvements in both motor and non-motor symptoms at 6 months post transplantation, indicating progressive graft maturation and functional integration. Along with the favorable safety profile, these data are consistent with the phase 1 results, suggesting NouvNeu001 as a promising disease-modifying therapy for Parkinson's disease.

Disclosures: H. Chen: None. **C. Niu:** None. **N. Xiong:** None. **N. Xiong:** None. **H. Shang:** None. **M. Cai:** A. Employment/Salary (full or part-time):; iRegene Therapeutics Co., Ltd. **X. Ren:** A. Employment/Salary (full or part-time):; iRegene Therapeutics Co., Ltd. **R. Yan:** A. Employment/Salary (full or part-time):; iRegene Therapeutics Co., Ltd. **J. Wei:** A. Employment/Salary (full or part-time):; iRegene Therapeutics Co., Ltd.. E. Ownership Interest

(stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); iRegene Therapeutics Co., Ltd..

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.15/Y3

Topic:

Support: Wellcome Trust Discovery award 226645/Z/22/Z

Title: Volitional deep brain stimulation following brain-computer interface training for Parkinson’s disease

Authors: *J. ZHANG[1], J. SUH[3], P. L. DANIEL[4], P. A. STARR[2], J. A. HERRON[5], S. LITTLE[1]; [1]Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of California, San Francisco, Mill Valley, CA; [3]UCSF, San Francisco, CA; [4]Psychology, UC San Diego, La Jolla, CA; [5]Dept. of Neurolog. Surgery, Univ. of Washington, Seattle, WA

Abstract: Deep brain stimulation (DBS) is transforming from a static therapy toward adaptive systems that adjust stimulation based on neural biomarkers. However, the detection of reliable biomarkers that capture the multi-dimensional nature of complex symptoms is often challenging. Here we demonstrate volitional DBS (vDBS)—a paradigm in which patients use brain-computer interface (BCI) training to learn self-regulation of a neural signal that then controls closed-loop DBS. Two patients with Parkinson’s disease implanted with sensing-enabled neurostimulators completed chronic, at-home BCI training by playing an airplane simulation game. Through training, they were able to effectively down-regulate their cortical beta signal (p’s < 1e-10), represented as the real-time position of a plane in the BCI game. Following training, this cortical beta signal served as the input to a closed-loop DBS algorithm. By modulating their beta signal to cross personalized thresholds, patients voluntarily increased or decreased neurostimulation amplitude at will, in the absence of physical movement (p’s < 1e-10). This proof-of-principle demonstration establishes that volitional control of intracranial neurostimulation is achievable without the need of an externalized manual controller. BCI-vDBS could potentially be used for a range of neuropsychiatric conditions and brain rehabilitation to support personalized control of neurostimulation.

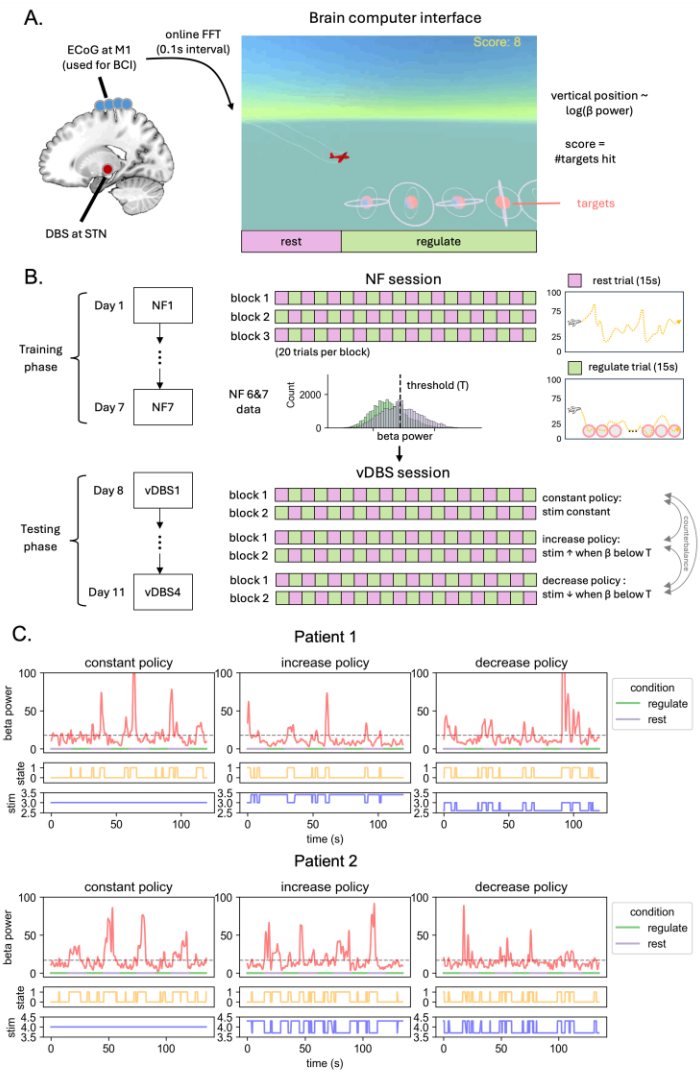


Fig. 1. (A) The BCI airplane simulation game. Two right-handed patients were chronically implanted with bilateral electrocorticography (ECoG) at the sensorimotor cortex and sensing-enabled deep brain stimulation (DBS) lead at the subthalamic nucleus (STN). The vertical position of the plane reflects the log beta power at the left primary motor cortex (M1) channel in real time. The game has 'rest' trials and 'regulate' trials (see Methods). Participants are required not to make physical movements and are videotaped during the game to check for immobility.

(B) Experiment procedure consists of a training phase of 7 neurofeedback (NF) sessions on constant DBS + a testing phase of 4 volitional DBS (vDBS) sessions. Each NF session consists of 3 blocks, with 10 'rest' trials and 10 'regulate' trials in an interleaved order in each block. Data during the last two NF sessions (i.e. NF 6 and 7) were used to determine the best beta threshold (T) for later aDBS tests. Each aDBS session consists of 2 blocks of 'constant' policy, 2 blocks of 'increase' vDBS policy, and 2 blocks of 'decrease' vDBS policy (see Methods). The order of the 3 policies was counterbalanced across vDBS sessions.

(C) Temporal dynamics of cortical beta power, its beta state, and stimulation amplitude under the vDBS policies. State 0 indicates a low beta state and state 1 indicates a high beta state. Dashed lines indicate the personalized threshold of beta power.

Disclosures: J. Zhang: None. **J. Suh:** None. **P.L. Daniel:** None. **P.A. Starr:** None. **J.A. Herron:** None. **S. Little:** None.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.16/Y4

Topic:

Support: Fondazione Pezzoli per la Malattia di Parkinson – ETS
Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) Project-ID 424778381 - TRR 295

Title: Riding the Wave: Autotuning Algorithm for Adaptive Deep Brain Stimulation in Parkinson's Disease

Authors: ***P. SERRAO**[1], L. CAFFI[2], F. LUISO[1,2], C. PALMISANO[2], L. ROSSI[3], M. ARLOTTI[3], I. U. ISAIAS[2,1];
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Abstract: Parkinson's disease (PD) is the fastest-growing neurodegenerative disorder worldwide. Deep brain stimulation (DBS) is an established treatment for advanced PD. Adaptive DBS (aDBS) of the subthalamic nucleus (STN) modulates stimulation amplitude according to STN local field potentials (LFP), targeting the beta-band (13-30Hz) activity. Effective aDBS requires accurate beta-power thresholds, but long-term changes in beta-power distributions currently require repeated in-person reprogramming. This study evaluates an automatic threshold-adjustment algorithm for chronic aDBS. Chronic STN-LFPs were recorded in 10 patients with idiopathic PD (age: 60±8 years) implanted bilaterally with the AlphaDBS IPG. Recordings lasted 350±145 days. Neural data had a 1-min resolution. AlphaDBS linearly modulates current amplitude minute-by-minute between clinically defined limits (Amin, Amax) according to beta-power thresholds (Pmin, Pmax). We implemented and simulated an autotuning algorithm that iteratively recalculated beta-power distributions within a moving window and updated Pmin/Pmax using predefined percentiles (i.e., 20th and 80th percentiles). Different window widths and update intervals were tested. Performance was assessed by average proximity to a target current distribution (20% Amin, 60% linear modulation, 20% Amax), variability, RMSE, changepoint analysis, and periodogram analysis. Statistical comparisons with the clinically delivered current were performed using Wilcoxon signed-rank tests ($p<0.05$). The optimal configuration, balancing performance and implementation constraints, consisted of a 24-hour moving window and a 1-hour update interval. Compared with the clinically delivered current, autotuning produced current distributions significantly closer to the target distribution, with lower variability and lower RMSE (all $p=0.002$). Changepoint analysis showed significantly greater long-term stability of current delivery ($p=0.002$). Periodogram analysis demonstrated that autotuning behaved similarly to a high-pass filter with a cutoff frequency of approximately 24 hours. This autotuning strategy may provide an effective and readily implementable solution for maintaining clinically meaningful aDBS operation over time while reducing suboptimal stimulation periods and unnecessary hospital visits. The approach preserves and enhances physiological circadian STN-LFP beta fluctuations, linked to sleep-wake cycles, dopaminergic medication, and motor fluctuations, while suppressing slower neural drifts that progressively shift the system away from its optimal operating point.

Disclosures: P. Serrao: None. **L. Caffi:** None. **F. Luiso:** None. **C. Palmisano:** 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.; Medtronic Inc., Minneapolis, Minnesota, USA. **L. Rossi:** A. Employment/Salary (full or part-time):; Newronika S.p.A., Milan, Italy. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Newronika S.p.A., Milan, Italy. **M. Arlotti:** A. Employment/Salary (full or part-time):; Newronika S.p.A., Milan, Italy. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); Newronika S.p.A., Milan, Italy. **I.U. Isaias:** 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.; Medtronic Inc., Minneapolis, Minnesota, USA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Newronika S.p.A., Milan, Italy. F. Consulting Fees (e.g., advisory boards); Newronika S.p.A., Milan, Italy.

Poster

PSTR265: Parkinson's Disease: Clinical Trials

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR265.17/Y5

Topic: I.04. Executive Functions

Title: Effects of Outreach Sessions on Cognition in Parkinson's disease

Authors: *B. TUBELO;
Kinesiology and Hlth., Iowa State Univ., Ames, IA

Abstract: Title: Effects of Outreach Sessions on Cognition in Parkinson's diseaseParkinson's disease (PD) is a neurodegenerative disease associated with motor symptoms as well as cognitive impairment, including deficits in attention, working memory, and executive function. Previous research has demonstrated that exercise interventions can improve cognitive performance in individuals with PD, particularly in measures of attention and working memory (David et al., 2015). Community-based outreach programs using adjuvant therapies such as boxing, singing, and dance have become increasingly popular among individuals with PD and have shown benefits for motor function, quality of life, and social engagement. However, the immediate effects of participation on these activities on cognitive function remain unclear. This study aims to investigate whether participation in boxing, singing, and dance outreach sessions influences cognitive function in individuals with Parkinson's disease.Participants aged between 50-85 years with a diagnosis of idiopathic PD, completed cognitive the Digit-Span Forward and Backward Test, and the Stroop Task before and after a one-hour boxing, singing, and dance outreach sessions. We hypothesized that participation in these outreach sessions will result in acute improvements in cognitive performance.Preliminary results on three participants demonstrated an improvement, though not significant, on all three cognitive measures. Data collection is ongoing to increase power and further investigate this current trend in the results.This study provides preliminary evidence on the effects of adjuvant therapies on cognitive impairment among individuals with PD.

Disclosures: B. Tubelo: None.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.01/Web Only

Topic: C.06. Neuromuscular Diseases

Support: Grifols

Title: Efficacy and Sustained Effects of Intravenous Immunoglobulin in Post-Polio Syndrome: Results from the Randomized, Placebo-Controlled FORCE Trial

Authors: *M. DALAKAS[1], D. TROJAN[2], H. ANDERSEN[3], J. JAKOBSEN[4], P. SÁIZ[5], J. SKOPEK[6], S. PETRI[7], K. PIASECKA–STRYCZYńSKA[8], L. BERTOLASI[9], K. REJDAK[10], S. CAMPRUBI[11], B. GARCIA[11], D. WHYMS[13], E. MONDOU[12], F. NOLLET[14];
[1]Thomas Jefferson Univ., Philadelphia, PA; [2]Dept. of Neurol. and Neurosurgery, Montreal Neurolog. Institute-Hospital, McGill Univ., Montreal, QC, Canada; [3]Århus Universitets Hosp., Aarhus, Denmark; [4]The Neurosci. Ctr. Rigshospitalet (National Hospital), Copenhagen Ø, Denmark; [5]Hosp. de Neurorehabilitación, Badalona, Spain; [6]Fakultní Thomayerova nemocnice, Praha, Czech Republic; [7]Hannover Med. Sch., Hannover, Germany; [8]Clin. Res. Ctr. Spólka z Ograniczona Odpowiedzialnoscia MEDIC-R Sp. K, Poznan, Poland; [9]Azienda Ospedaliera Universitaria Integrata Verona (Ospedale Borgo Roma), Verona, Italy; [10]Dept. of Neurol., Med. Univ. of Lublin, Lublin, Poland; [11]Grifols, Barcelona, Spain; [12]Grifols, Research Triangle Park, NC; [13]Grifols Worldwide Operations, Dublin, Ireland; [14]Dept. of Rehabil. Med., Amsterdam UMC Location Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Post-polio syndrome (PPS) is a chronic motor neuron disorder marked by progressive weakness and frequently a decline in walking capacity, with no disease-modifying pharmacological treatment available. The FORCE trial was a Phase II/III multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and durability of intravenous immunoglobulin (IVIG) in adults with PPS. Following adaptive dose selection, participants were randomized to IVIG 1 g/kg (n=75) or placebo (n=74) administered every four weeks for 52 weeks, followed by a treatment-free observation period of 24 weeks. The primary endpoint was change from baseline in two-minute walking distance (2MWD; baseline mean 107.6 m for IVIG group vs 106.4 m for placebo), representing short-duration walking performance; secondary and exploratory endpoints included six-minute walking distance (6MWD), muscle strength assessed by Medical Research Council scale, and fatigue by Fatigue Severity Scale. Analyses were performed using mixed models for repeated measures. At Week 52, IVIG significantly improved 2MWD versus placebo (adjusted p=0.0469), with a sensitivity analysis showing a greater mean improvement from baseline with IVIG compared to placebo (12.8 m vs 6.7 m), equating to a least-squares mean difference (LSMD) of +6.1 m (p=0.0147). Importantly, improved walking performance persisted at Week 64 (12 weeks after treatment cessation), with a LSMD of +5.7 m favoring IVIG (p=0.0190), before efficacy attenuation by Week 76. Endurance assessed by 6MWD showed numerically greater improvement with IVIG at Week 52 (LSMD +15.8 m; p=0.1205) and demonstrated a sustained benefit during follow-up at Week 64 (LSMD +21.2 m; p=0.0433), with partial loss of effect by Week 76. Manual muscle testing showed improved strength with IVIG compared with decline

under placebo (LSMD +0.61; p=0.0220), while fatigue severity decreased numerically more with IVIG (LSMD −0.35; p=0.0803), consistent with functional improvement at week 52. At the end of follow-up (Week 76), between-group differences in both measures were no longer evident, consistent with attenuation of treatment effects after cessation. IVIG was generally well tolerated, with treatment-emergent adverse events consistent with the known safety profile. These findings indicate that IVIG improves walking performance in PPS and produces sustained functional benefits beyond active treatment, supporting durability of effect on motor function in such a chronic slowly progressive motor neuron disorder as PPS for 12 weeks.

Disclosures: M. Dalakas: None. **D. Trojan:** 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.; Grifols. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); the Polio Quebec Association and The Robert Lassner Research Fund. F. Consulting Fees (e.g., advisory boards); Grifols. **H. Andersen:** F. Consulting Fees (e.g., advisory boards); CSL Behring, NMD Pharma, Pfizer, Novo, Lundeck, Alexion, Sanofi Genzyme, Biogen, Merck, UCB Pharma. **J. Jakobsen:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Takeda. **P. Sáiz:** None. **J. Skopek:** None. **S. Petri:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); DGM e.V., Federal Ministry of Education and Research, German Israeli Foundation for Scientific Research and Development, EU Joint Programme for Neurodegenerative Disease Research, Neurodegenerative Research Inc.. F. Consulting Fees (e.g., advisory boards); Biogen, Roche, Amylyx, Ferrer, Desitin, Italfarmaco, Zambon. **K. Piasecka–Stryczyńska:** None. **L. Bertolasi:** None. **K. Rejdak:** None. **S. Camprubi:** A. Employment/Salary (full or part-time):; Grifols. **B. Garcia:** A. Employment/Salary (full or part-time):; Grifols. **D. Whyms:** A. Employment/Salary (full or part-time):; Grifols Worldwide Operations. **E. Mondou:** A. Employment/Salary (full or part-time):; Grifols. **F. Nollet:** 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.; Grifols. F. Consulting Fees (e.g., advisory boards); Grifols.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.02/Web Only

Topic: C.06. Neuromuscular Diseases

Support: KAKENHI JP 23K06976

Title: AR PROTAC ARV-110 ameliorates motor dysfunction in a mouse model of spinal and bulbar muscular atroph

Authors: *H. ADACHI[1], Z. HUANG[2], E. BAT-ERDENE[2];
[1]Univ. of Occup. and Envrn. Health, Japan, Kitakyushu, Japan; [2]Dept. of Neurol., Univ. of Occup. and Envrn. Health, Japan, Kitakyushu, Japan

Abstract: [Background] Polyglutamine (polyQ) diseases are inherited neurodegenerative diseases caused by the expansion of a polyQ tract within the causative genes. In chronic neurodegenerative disorders such as polyQ diseases, commonly observed phenotypes include the abnormal accumulation of disease-causing proteins and the formation of nuclear and cytoplasmic inclusions. Under pathologic conditions, the accumulated level of misfolded and toxic proteins may exceed the protective ability of the proteolytic machinery; the inability to either maintain misfolded proteins in a soluble form or degrade them results in their accumulation and the formation of inclusions. Spinal and bulbar muscular atrophy (SBMA) is a hereditary motor neuron disease caused by the expansion of CAG repeats in the first exon of androgen receptor (AR) gene. Currently, the only disease-modifying treatment available for SBMA is leuprorelin, and if this drug cannot be used due to side effects, patients will only receive symptomatic treatments. Here, we explore one alternative therapeutic strategy by using AR-targeted proteolysis-targeting chimeras (PROTACs), a class of bifunctional small molecules that were initially developed to promote degradation of the AR protein in individuals with prostate cancer. In this study, we attempted to develop a novel disease-modifying therapy using the AR PROTAC ARV-110.[Materials and Methods] To determine whether normal and mutant AR are degraded by ARV-110, we induced PC12 cells expressing normal human AR (10Q) and mutant AR (112Q) with doxycycline and ligands, and transiently transfected wild-type (AR-20Q) or mutant (AR-76Q) AR into Neuro2A cells and treated these cells with ARV-110. Male AR-24Q or AR-97Q mice were orally administered ARV-110 at doses of 1.5 mg/kg or 3 mg/kg daily from 6 to 25 weeks of age, and various neurological and behavioral parameters were assessed. Control mice were administered methylcellulose.[Results] Immunoblot analysis demonstrated a significant reduction of wild-type (AR-20Q or AR-10Q) and mutant (AR-76Q or AR-112Q) in both cell models treated with ARV-110 ($p < 0.0001$). ARV-110 treatment showed improvement of motor dysfunction, alleviated body weight loss and enhanced survival rate in comparison with vehicle treated SBMA transgenic mice ($p < 0.001$). Furthermore, ARV-110 treatment attenuated muscle pathology and reduced levels of monomeric and aggregated mutant AR protein in the skeletal muscles ($p < 0.001$).[Conclusions] Overall, our findings highlight that ARV-110 may be used as a novel treatment for SBMA if the dosage is carefully optimized to avoid side effects.

Disclosures: H. Adachi: None. **Z. Huang:** None. **E. Bat-Erdene:** None.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

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Program #/Poster #: PSTR266.03/Y6

Topic: C.06. Neuromuscular Diseases

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Title: Glucoraphenin Protects Against Oxidative Stress-Induced Spinal Neuronal Injury and Dexamethasone-Induced Myotube Degeneration

Authors: *W. JEON, J. HONG, H. KIM, J. LEE, C. YEO, H. KIM, Y.-S. LEE;
Jaseng Med. Fndn., Seoul, Korea, Republic of

Abstract: Glucoraphenin, a major glucosinolate found in radish (Raphanus sativus) seeds, is a precursor of sulforaphene and has been reported to possess antioxidant and cytoprotective properties. However, its potential role in protecting neuronal and neuromuscular cells under pathological stress conditions remains unclear. The present study investigated the neuroprotective and anti-atrophic effects of glucoraphenin using models of oxidative stress-induced spinal neuronal injury and dexamethasone (DEX)-induced skeletal muscle degeneration. Primary spinal cord neurons isolated from embryonic day 15 Sprague-Dawley rat embryos were exposed to hydrogen peroxide (H_2O_2)-induced oxidative stress in the presence or absence of glucoraphenin (1-10 μM). Neuronal viability was evaluated using a CCK-8 assay, and neurite outgrowth was assessed by βIII-tubulin (Tuj1) immunofluorescence staining. In parallel, differentiated C2C12 myotubes were treated with DEX (200 μM) with or without glucoraphenin. Myotube morphology, myogenic regulatory factors, protein synthesis- and degradation-related pathways, oxidative stress markers, and mitochondrial function were evaluated. Glucoraphenin showed no cytotoxicity up to 800 μM and concentrations of 1, 5, and 10 μM were selected for subsequent experiments. Glucoraphenin protected primary spinal cord neurons against H_2O_2-induced oxidative injury and improved neuronal viability. In addition, Tuj1 immunostaining demonstrated enhanced neurite outgrowth in glucoraphenin-treated neurons. In DEX-treated C2C12 myotubes, glucoraphenin preserved myotube morphology and attenuated myotube degeneration. Glucoraphenin restored the expression of myogenic regulatory factors, enhanced protein synthesis-associated signaling, suppressed protein degradation-associated markers, reduced oxidative stress, and improved mitochondrial function. These findings demonstrate that glucoraphenin exerts dual protective effects on primary spinal cord neurons and skeletal muscle cells under stress conditions. The present study provides evidence that glucoraphenin promotes neuronal resilience while attenuating muscle degeneration, highlighting its potential as a neuromuscular protective phytochemical. Collectively, these findings support further investigation of glucoraphenin as a functional food-derived bioactive compound for maintaining neuromuscular health and mitigating stress-associated neuronal and muscular dysfunction.

Disclosures: W. Jeon: None. **J. Hong:** None. **H. Kim:** None. **J. Lee:** None. **C. Yeo:** None. **H. Kim:** None. **Y. Lee:** None.

Poster

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Support: This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number RS-2024-00444687).

Title: Raphanus sativus L. Seed Extract Preserves Neuromuscular function by Attenuating Dexamethasone-Induced Muscle Atrophy and Oxidative Stress-Induced Neuronal Damage

Authors: *C. YEO, J. HONG, H. KIM, W. JEON, J. LEE, H. KIM, Y.-S. LEE;
Jaseng Med. Fndn., Seoul, Korea, Republic of

Abstract: Neuromuscular dysfunction is characterized by the concurrent deterioration of neuronal integrity and skeletal muscle homeostasis, processes that are frequently driven by oxidative stress and chronic catabolic signaling. Identifying interventions capable of simultaneously protecting neurons and skeletal muscle may provide a promising strategy for preserving neuromuscular function. Raphanus sativus Linne extract (RSL) contain various phytochemicals, including glucoraphenin and other glucosinolate derivatives, which have been reported to exert antioxidant and anti-inflammatory effects. However, the potential protective effects of RSL against oxidative stress-associated neuronal injury and glucocorticoid-induced skeletal muscle atrophy remain unclear. This study aims to evaluate the neuroprotective and anti-atrophic effects of RSL using complementary neuronal and skeletal muscle injury models. To evaluate the neuroprotective effects of RSL, primary spinal cord neurons will be exposed to 100 μM H_2O_2 to induce oxidative stress-mediated neuronal injury. RSL will first be screened over a concentration range up to 200 μg/ml using a CCK-8 assay to evaluate cytotoxicity and determine optimal treatment concentrations, and neurite outgrowth was quantified to evaluate neuronal regeneration using βIII-tubulin (Tuj1) immunofluorescence staining. For the assessment of anti-atrophic effect, C2C12 myotubes were treated with 200 μM dexamethasone (DEX) in the presence or absence of RSL. Myotube diameter and nubmer was measured by MHC immunofluorescence staining, and the expression of myogenic markers (MyoD, MyoG, and MHC), atrophy-related proteins (MuRF1 and Atrogin-1), and signaling molecules involved in muscle protein synthesis and degradation pathways was analyzed. RSL significantly protected spinal neurons against H2O2-induced oxidative damage, as evidenced by increased neurite outgrowth compared with the H2O2-treated group. In C2C12 myotubes, RSL markedly attenuated muscle atrophy by increasing the expression of myogenic markers, including MyoD, MyoG, and MHC, while suppressing the expression of the muscle atrophy-related proteins Atrogin-1 and MuRF1. Furthermore, RSL significantly increased myotube diameter and number compared with the DEX-treated group. Collectively, these findings suggest that RSL preserves neuromuscular integrity by protecting neurons from oxidative stress-induced injury while attenuating skeletal muscle atrophy. Through coordinated neuroprotective and anti-atrophic actions, RSL may represent a promising therapeutic strategy for oxidative stress-associated neuromuscular disorders.

Disclosures: C. Yeo: None. **J. Hong:** None. **H. Kim:** None. **W. Jeon:** None. **J. Lee:** None. **H. Kim:** None. **Y. Lee:** None.

Poster

PSTR266: Other Neuromuscular Diseases

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Title: PDRN Pharmacopuncture Protects Against Dexamethasone-Induced Neuromuscular Dysfunction Through Antioxidant, Myogenic, and Neuroprotective Mechanisms

Authors: *J. LEE, Y. LEE;
Jaseng Med. Fndn., Seoul, Korea, Republic of

Abstract: Oxidative stress is a key contributor to both skeletal muscle atrophy and peripheral neuronal dysfunction. Polydeoxyribonucleotide pharmacopuncture solution (PDRN-PS) possesses anti-inflammatory and tissue-protective properties; however, its neuroprotective and myoprotective effects in oxidative stress-associated neuromuscular disorders remain unclear. This study investigated the effects of PDRN-PS on oxidative stress-induced neuronal injury in dorsal root ganglion (DRG) neurons and dexamethasone (Dexa)-induced muscle atrophy using complementary in vitro and in vivo models. Primary DRG neurons were exposed to hydrogen peroxide (H_2O_2) to induce oxidative injury. Cell viability was assessed using a CCK-8 assay, and neurite outgrowth was quantified by TUJ1 immunocytochemistry. PDRN-PS (1-100 μg/ml) significantly increased DRG cell viability under both basal and oxidative stress conditions. In H_2O_2-challenged cultures, significant protection was observed even at the lowest concentration tested (1 μg/ml). Based on dose-response screening, 1, 5, and 10 μg/ml were selected for neurite analysis. PDRN-PS dose-dependently enhanced total, mean, and maximum neurite length compared with H_2O_2-treated controls, indicating neuroprotective and neuritogenic effects. In C2C12 myotubes, PDRN-PS increased myotube diameter and reduced Dexa-induced intracellular reactive oxygen species (ROS) accumulation in a dose-dependent manner. For in vivo validation, PDRN-PS was injected intramuscularly into the gastrocnemius during DEX treatment across four groups: Sham, DEX (25 mg/kg), PDRN-L (0.047 mg/day), and PDRN-H (0.094 mg/day). Compared with the Dexa-only group, PDRN-PS significantly improved body weight, treadmill performance, gastrocnemius muscle mass index, muscle fiber cross-sectional area, and minimum Feret's diameter. Oxidative stress was attenuated, as evidenced by reduced MDA and 4-HNE levels and restoration of GSH content. Molecular analyses further indicated activation of antioxidant defense pathways, including Nrf1, SOD1, catalase, and HO-1. In parallel, PDRN-PS enhanced the expression of myogenic regulators (IGF-1, MyoD1, and myogenin) while suppressing muscle atrophy-associated factors (MuRF1 and Atrogin-1). These findings suggest that PDRN-PS preserves skeletal muscle through coordinated antioxidant,

anabolic, and anti-atrophic mechanisms. Collectively, these findings demonstrate that PDRN-PS exerts both neuroprotective and myoprotective effects under oxidative stress conditions and attenuates dexamethasone-induced muscle atrophy through coordinated antioxidant and pro-myogenic mechanisms.

Disclosures: J. Lee: None. **Y. Lee:** None.

Poster

PSTR266: Other Neuromuscular Diseases

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Program #/Poster #: PSTR266.06/Y9

Topic: C.06. Neuromuscular Diseases

Support: NIH R01 NS131402

Title: Functional Characterization of Neuropathy, Arthropathy and Skeletal Dysplasia-Causing TRPV4 Variants

Authors: *M. ZERISENAI[1], A. MEEKER[2], L. VO[3], A. HERMAN[4], B. A. MCCRAY[3];
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[3]Neurol., [4]Cell. and Mol. Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: Background: Mutations in the TRPV4 calcium permeable ion channel lead to three categories ofdiseases including forms of peripheral neuropathy, skeletal dysplasia, and arthropathy. Thesemutations have gain-of-function effects leading to an influx of calcium and downstream cellulartoxicity. It is unknown how different mutations in the same gene cause different diseases.However, these mutations seem to segregate in specific domains of the protein suggestingdistinct functional effects lead to the development of three different disease states. Wehypothesize that mutations causing peripheral neuropathy, skeletal dysplasia, and arthropathymay have different effects on TRPV4 ion channel activity, subcellular localization, andprotein-protein interactions.**Methods:** To study functional properties of TRPV4, we utilized transient transfection withGFP-tagged wild-type (WT)or mutant forms of TRPV4 from each type of channelopathy andtransfected motor neuron cells (MN-1),canine kidney epithelial cells (MDCK),and humanembryonic kidney cells (HEK293T).We analyzed ion-channel activity at baseline and afteradministration of a hypotonic solution using ratiometric calcium imaging with Fura-2 AMcalcium indicator. We assessed subcellular localization of TRPV4 using immunofluorescencemicroscopy and flow cytometry. RhoA binding was also assessed using co-immunoprecipitation.**Results:** Neuropathy variants had baseline calcium levels similar to WT, whereas skeletaldysplasia and arthropathy mutants had higher baseline levels. Once stimulated, neuropathy andskeletal dysplasia variants showed significantly elevated calcium levels whereas arthropathymutants showed elevated levels but to a lesser extent. With respect to subcellular localization, allarthropathy and most skeletal dysplasia variants show reduced cell surface expression, whereasneuropathy variants show cell surface localization similar to WT. We further

showed thatvariants with reduced surface expression instead localize to the endoplasmic reticulum.Additionally, we found that skeletal dysplasia variants still bind the RhoA protein, while bindingis reduced in neuropathy and arthropathy mutants.**Conclusion:** Pathogenic TRPV4 variants underlying three different disease phenotypes exhibitunique signatures of ion channel activity and localization. These findings indicate that skeletaldysplasia and arthropathy TRPV4 variants exhibit elevated calcium levels while subsequentlydemonstrating subcellular internalization. These different functional signatures may contribute todistinct downstream effects on TRPV4 function and disease pathogenesis.

Disclosures: M. Zerisenai: None. **A. Meeker:** None. **L. Vo:** None. **A. Herman:** None. **B.A. McCray:** 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.; Collaborator with Actio Biosciences.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

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Program #/Poster #: PSTR266.07/Y10

Topic: C.06. Neuromuscular Diseases

Support: 5F31NS141427-02

Title: Involvement of motor neuron mitochondria in charcot-marie tooth type 2d (cmt2d)

Authors: *J. FUNKE[1], R. W. BURGESS[2];
[1]The Jackson Lab., Ellsworth, ME; [2]The Jackson Lab., Bar Harbor, ME

Abstract: Mutations in genes encoding mitochondrial proteins often cause peripheral neuropathy, including multiple subtypes of Charcot-Marie-Tooth (CMT). Mutations in *GARS* cause CMT type 2D. *GARS* encodes glycyl tRNA-synthetase, which is bifunctional: the gene encodes for both the cytosolic and mitochondrial versions. Mouse models of CMT2D exhibit a robust phenotype that impacts mitochondria in a cell-type specific manner. We used biochemical assays, immunofluorescence, and electron microscopy to assess mitochondrial quantity and morphology in neuronal cell bodies, axons and nerve terminals of affected motor neurons, and in unaffected cell types/tissues, of *Gars* mice. Mitochondria were also isolated for proteomics. Mitochondria in motor neurons were targeted using a system that allows the cell-type-specific isolation of mitochondria via a Cre-inducible GFP-tagged outer membrane protein. We found that the distal axon, and the neuromuscular junction (synapse), of motor neurons in *Gars* mice exhibit significantly reduced mitochondrial number as compared to WT. As well, motor neuron soma also have reductions in mitochondrial quantity - indicating that the entire motor neuron is impacted. Axonal mitochondrial morphology was unaltered, but reduced mitochondrial cristae density was found in motor neuron soma. Proteomics results identified 138 differently expressed

mitochondrial-specific proteins (mtDEP) in *Gars* motor neuron mitochondria as compared to WT. Only 18 mtDEPS were found in the bulk mitochondrial proteome (i.e. all mitochondria in the spinal cord), confirming the cell-type specific phenotype. Additional validation of mtDEPs, as well as examination at different ages and in unaffected cell types, is under progress. Mitochondria are affected in a cell-type specific manner in *Gars* mice, like cell-type specific alterations involving cytosolic translation in these mice. Additionally, motor neurons are affected across all cellular compartments, indicating that mitochondria may be impacted directly due to gene function. As well, this could partially explain length dependent neuropathy and synaptic deficits observed in *Gars* mice.

Disclosures: J. Funke: None. **R.W. Burgess:** None.

Poster

PSTR266: Other Neuromuscular Diseases

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant RM1NS143850

Title: CRISPR-dCas9-Mediated Frataxin Gene-Targeted Histone Demethylation Upregulates Frataxin Gene Expression by Contracting GAA Repeat in Friedreich's Ataxia

Authors: *S. SENGUPTA[1], R. ARMBRISTER[2], Y. LIU[3];
[1]Biochem., [3]Chem. and Biochem., [2]Florida Intl. Univ., Miami, FL

Abstract: Friedreich's ataxia (FRDA) is a genetic neurodegenerative disorder caused by GAA repeat expansion in intron 1 of the frataxin (FXN) gene, causing FXN gene silencing via the formation of heterochromatinization and R-loops on the expanded repeats. Frataxin deficiency leads to mitochondrial dysfunction, oxidative stress, and accumulation of oxidative DNA damage. Currently, no cure is available for FRDA due to the inherited expanded GAA repeats in patient's genome. Studies from our group have shown that the DNA base excision repair (BER) pathway can interplay with the inhibition of histone methylation to contract the expanded GAA repeats by removing DNA damage in FRDA cells and mice. We further hypothesize that FXN gene-targeted histone demethylation can crosstalk with BER to contract the expanded GAA repeats, leading to the upregulation of the FXN gene in FRDA. To test this hypothesis, we developed a plasmid-based FXN gene-targeted CRISPR/dCas9-mediated H3K9 demethylation system containing dCas9-histone H3K9 demethylase KDM4D fusion protein with five different guide RNAs (gRNAs) that target various regions flanking the expanded GAA repeats. We found that targeting pdCas9-KDM4D to the region at 55 bp (gRNA3) upstream of the expanded GAA repeats at the FXN gene led to GAA repeat contraction, increasing Fxn protein level in FRDA neural cells by 2-3-fold. We further demonstrated that dCas9-KDM4D fusion protein targeted to the regions at 316 bp (gRNA1), 215 bp (gRNA1) exhibited no effects on the upregulation of Fxn

protein level on FRDA neural cells. In contrast, the fusion protein targeted to the regions at 55 bp upstream of GAA repeats and 3 bp and 264 bp downstream of the repeats significantly increased the Fxn protein level in FRDA neural cells, with the fusion protein targeted by gRNA3 exhibiting the highest effects in increasing Fxn level in FRDA neural cells. The results indicated that FXN gene-targeted histone H3K9 demethylation upregulated the FXN gene by contracting the expanded GAA repeats in a gene target region-dependent manner. Our study provides the first evidence that the FXN gene-targeted histone epigenetic editing can contract GAA repeats to increase frataxin gene expression in FRDA neural cells, opening a novel avenue for gene therapy for FRDA and other trinucleotide repeat expansion diseases.

Disclosures: S. Sengupta: None. **R. Armbrister:** None. **Y. Liu:** None.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

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Program #/Poster #: PSTR266.09/Y12

Topic: C.06. Neuromuscular Diseases

Title: Preserved propriosensory connectivity masks functional deficits in the stretch reflex arc of CMT1A mice.

Authors: E. SMITH[1], C. CASIANO-RIVERA[2], ***T. M. ROTTERMAN**[1];
[1]Pharmacology, Physiol. & Biophysics, [2]Grad. Program of Neurosci., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Charcot-Marie-Tooth disease type 1A (CMT1A) results from duplication of the peripheral myelin protein 22 gene (*PMP22*) which leads to abnormal myelination of peripheral axons. *Pmp22* duplication mice recapitulate human disease showing reduced conduction velocities and impaired sensory-motor behaviors. We previously showed that abnormal peripheral axon connectivity in CMT type 2D leads to central degeneration of propriosensory Ia-motoneuron synapses and ultimately a loss of the monosynaptic stretch reflex. In this project, we investigated whether CMT1A, the most common form of CMT, similarly showed a loss of propriosensory Ia-motoneuron connectivity and impairments in the stretch reflex. In order to investigate this, we injected 3-month-old transgenic *Pmp22* overexpressing mice and wild-type littermate controls with a fluorescent tracer to retrogradely label motoneurons innervating hindlimb muscles. We then performed terminal electrophysiology recordings to measure stretch-evoked reflex responses and quantified muscle force generation as well as EMG activity. Spinal cords were then collected and processed for confocal imaging to quantify propriosensory Ia synaptic terminal density on 3D-reconstructed motoneurons. In contrast to CMT2D, PMP22 overexpressing mice anatomically retained normal propriosensory Ia synaptic connectivity compared to wild-type controls. However, PMP22 mutants showed significant impairments in stretch-evoked reflex responses and reduced EMG activity. These findings suggest that, despite

retained anatomical synaptic structures, functional deficits in the reflex arc occur in adult PMP22 mutant mice that are yet to be fully characterized.

Disclosures: E. Smith: None. **C. Casiano-Rivera:** None. **T.M. Rotterman:** None.

Poster

PSTR266: Other Neuromuscular Diseases

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.10/Y13

Topic: C.06. Neuromuscular Diseases

Title: Developmental vulnerability of propriosensory circuits in CMT2D: normal synaptogenesis followed by selective degeneration

Authors: *C. V. CASIANO-RIVERA[1], E. SMITH[2], T. M. ROTTERMAN[2];
[1]Grad. Program of Neurosci., [2]Pharmacology, Physiol. & Biophysics, Boston Univ., Boston, MA

Abstract: Charcot-Marie-Tooth disease type 2D (CMT2D) results from missense and in-frame mutations in the glycyl-tRNA synthetase gene (*Gars*), leading to peripheral axon degeneration. Such mutations can cause partial neuromuscular junction denervation, resulting in muscle weakness and atrophy. In this project we further demonstrate that $Gars^{\Delta ETAQ}$ mice exhibit impaired sensory-guided movements, proprioceptive deficits, and postural instability using machine-learning based automated behavioral analyses. These behavioral deficits in-turn correlate with both peripheral and central degeneration of propriosensory Ia afferents, which are responsible for initiating the monosynaptic stretch reflex. We therefore asked the fundamental question, do propriosensory Ia connections form normally during development in $Gars^{\Delta ETAQ}$ mice? To address this, we injected a fluorescent tracer into hindlimb muscles to retrogradely label motoneurons in the spinal cord. Mice were perfused at postnatal days P4, P12, P21, and P45 to investigate specific developmental timepoints of Ia-motoneuron synapse maturation and plasticity. Spinal cords were processed and confocal imaged to quantify Ia synaptic terminals on the soma and proximal dendrites of 3D-reconstructed motoneurons. Preliminary findings demonstrate comparable somatic and dendritic Ia synaptic densities between wild-type and $Gars^{\Delta ETAQ}$ mice atP4. By P12, peripheral Ia afferent denervation occurs at the muscle spindle and by P21 central loss of Ia-motoneuron connectivity is detected and further declines by P45. These data suggest that Ia-motoneuron connections form normally during early postnatal development in $Gars^{\Delta ETAQ}$ mice but begin to degenerate in the second to third postnatal week. Future electrophysiological studies will determine whether these Ia-motoneuron connections are functionally formed in early postnatal $Gars^{\Delta ETAQ}$ mice.

Disclosures: C.V. Casiano-Rivera: None. **E. Smith:** None. **T.M. Rotterman:** None.

Poster

PSTR266: Other Neuromuscular Diseases

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Program #/Poster #: PSTR266.11/Y14

Topic: C.06. Neuromuscular Diseases

Title: An AAV-expressed microdystrophin with an extended C-terminal domain rescues neuromuscular junction deficits in a mouse model of Duchenne Muscular Dystrophy

Authors: *B. P. HEITHOFF, C. PETERSEN, S. FOLTZ, J. D. GLENN, T. CHEN, J. YANG, Y. LIU, O. DANOS, J. B. SMITH;
REGENXBIO, Inc., Rockville, MD

Abstract: Duchenne Muscular Dystrophy (DMD) is a fatal, X-linked disease caused by mutations in the *DMD* gene resulting in loss of dystrophin protein. Lack of dystrophin causes a severe reduction in muscle fiber integrity but also results in aberrant neuromuscular junction (NMJ) morphology and function in both DMD (*mdx*) mice and human patients.
Dystrophin restorative therapies aim to address the underlying cause of DMD and protect muscle fibers from damage to slow disease progression. Gene replacement strategies using viral vectors to deliver truncated versions of dystrophin, termed "microdystrophins" (µDys), can restore muscle function in animal models. However, each of the clinical-stage µDys proteins have been designed to include different domains of dystrophin. Consequently, the differences in how each µDys compensates for dystrophin loss are expected to confer varying levels of improvement in DMD-associated phenotypes. RGX-202, REGENXBIO's investigational AAV gene therapy for DMD, utilizes a µDys construct containing an extended C terminal domain (CT), which yields greater µDys expression and improves muscle strength and resilience in *mdx* mice compared to a µDys lacking the CT (Foltz et al., 2025). Here, we extend our previous studies to determine if AAV-expressed µDys also improves the morphology and function of NMJs in the *mdx* mouse model of DMD, and whether this may be dependent on specific domains of dystrophin.
We compared three AAV vectors expressing different µDys constructs: (1) Hinge3 + extended CT domain (µDysH3-CT194), (2) Hinge3 without extended CT (µDysH3-CT48) and (3) Hinge2 without extended CT (µDysH2-CT48). Vectors were injected at 1e14 GC/kg via tail vein in 5-week-old *mdx* mice. Four weeks later, vector DNA, mRNA transcripts, and µDys protein levels were evaluated across all groups. NMJ morphology parameters were evaluated using bungarotoxin (BTX) to label acetylcholine receptors at the motor endplate in gastrocnemius and diaphragm. The µDys utilizing the µDysH3-CT194 showed significant rescue in all NMJ parameters assessed, resulting in a ~67% percentage of NMJs classified as "healthy" compared to *mdx* vehicle controls (~29% healthy) and wild type controls (~90% healthy). By comparison, both µDys constructs without the extended CT rescued ~45% of NMJs. snRNAseq analysis demonstrated expression of µDysH3-CT194 in ~45% of nuclei in the NMJ microdomains of the gastrocnemius muscle following vector administration at a clinically relevant dose of 1e14 GC/kg. Our results demonstrate that the RGX-202 µDys achieves superior rescue of the NMJ phenotypes in a DMD mouse model, potentially providing added benefit beyond muscle fiber preservation.

Disclosures: B.P. Heithoff: A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **C. Petersen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **S. Foltz:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **J.D. Glenn:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **T. Chen:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **J. Yang:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **Y. Liu:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **O. Danos:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc. **J.B. Smith:** A. Employment/Salary (full or part-time):; REGENXBIO, Inc..

Poster

PSTR266: Other Neuromuscular Diseases

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Topic: C.06. Neuromuscular Diseases

Support: NIH Grant K99NS146618
NIH Grant R01AR082852

Title: Timing-Dependent Reversibility of Neurological Deficits in a Neuronal Mouse Model of Myotonic Dystrophy Type 1

Authors: *L. NITSCHKE, T. COOPER;
Baylor Col. of Med., Houston, TX

Abstract: Myotonic Dystrophy Type 1 (DM1) is a progressive autosomal dominant disorder affecting 1 in 8,500 individuals. While traditionally characterized by skeletal muscle dysfunction, DM1 is increasingly recognized as a multisystemic disorder with significant neurological manifestations. Up to 80% of patients exhibit cognitive impairment, sleep disturbances, and neuropsychiatric symptoms, with congenital and childhood-onset cases showing the most severe neurological involvement. DM1 is caused by a CTG repeat expansion in *DMPK*, which produces CUG repeat RNA that sequesters the Muscleblind-Like (MBNL) family of RNA binding proteins leading to the dysregulation of RNA processing. While MBNL sequestration and mis-splicing of key MBNL targets have been shown to be responsible for the DM1 skeletal muscle phenotypes, the molecular mechanisms underlying DM1 neurological manifestations remain poorly understood, in part due to the lack of good experimental systems that recapitulate DM1 brain disease.
To fill this gap, we developed a doxycycline (dox)-repressible DM1 brain mouse model (CUG960) that uses the *NEFH* promoter to drive expression of CUG repeat RNA in neurons starting from embryonic development. CUG960 mice recapitulate key molecular DM1 features including nuclear RNA foci, MBNL sequestration, and dysregulation of alternative splicing. Phenotypically, CUG960 mice exhibit reduced brain weight and display behavioral abnormalities including deficits in contextual and spatial learning and memory, implicating hippocampal dysfunction. RNA sequencing of the hippocampus further identified 322 mis-

splicing events enriched for genes involved in synaptic function and neuronal integrity, including *Dlg2* (PSD-93) and *Mapt* (Tau), providing a possible molecular basis for the learning and memory deficits.
A key question for therapeutic development is whether neurological deficits in DM1 can be reversed. To address this, we suppressed CUG repeat RNA expression at conception, birth (P0), or 8 weeks of age by feeding mice dox-containing chow and assessed phenotypes at 6 months. Doxycycline treatment abolished CUG repeat RNA expression and rescued mis-splicing patterns at all timepoints. However, only early suppression at conception or P0 rescued structural and behavioral deficits, while adult suppression failed to do so. These findings reveal a critical therapeutic window in DM1 neurological disease and highlight the importance of early diagnosis and intervention. Future studies will investigate the molecular mechanisms underlying hippocampal dysfunction and define the basis for the irreversibility of neurological deficits in adulthood.

Disclosures: L. Nitschke: None. **T. Cooper:** None.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.13/Y16

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant AI093504
NIH Grant AI173059
NIH Grant AI180532
DTRA Grant HDTRA1-22-1-0029
DTRA Grant MCDC2201-002

Title: Human iPSC-derived neuromuscular junction organoids model Lambert-Eaton myasthenic syndrome through patient IgG-mediated Cav2.1 depletion

Authors: *C. AGUAYO, P. M. MCNUTT;
Wake Forest Inst. for Regenerative Med., Winston-Salem, NC

Abstract: The neuromuscular junction (NMJ) is a specialized synapse that mediates motor neuron control of skeletal muscle contraction. Lambert-Eaton myasthenic syndrome (LEMS) is a rare, often debilitating presynaptic autoimmune disorder affecting 1-3 per million individuals, in which patient antibodies target P/Q-type voltage-gated calcium channels (VGCCs), leading to reduced calcium influx, impaired acetylcholine release, and progressive muscle weakness. Despite its clinical severity, LEMS remains difficult to model in vivo, as passive-transfer rodent systems require large amounts of rare patient IgG and fail to fully capture human NMJ maturation and physiology. Human induced pluripotent stem cell-derived NMJ organoids provide a scalable, human-relevant platform to study antibody-mediated synaptic dysfunction

using limited patient material.Here, we optimized a human iPSC-derived NMJ organoid model to study LEMS through passive transfer of patient-derived IgG. NMJ organoids formed integrated motor neuron and skeletal muscle populations with acetylcholine receptor clustering and spontaneous electrophysiological activity. Exposure to IgG from two LEMS patients caused depletion of the P/Q-type VGCC subunit Cav2.1. Following 120 hr exposure to 100 nM LEMS IgG, Western blot analysis showed up to a 60% reduction in Cav2.1 protein compared with control IgG-treated organoids (n=7, p=0.0006). Immunocytochemistry further demonstrated an 80% reduction in VGCC/Cav2.1 signal under the same exposure conditions (n=5, p=0.0305), supporting antibody-mediated depletion of the presynaptic LEMS target.Functionally, multielectrode array recordings showed that 120 hr exposure to LEMS IgG reduced spontaneous neuronal firing by 2.5-fold. Continuous treatment with 30 μM 3,4-diaminopyridine (3,4-DAP), a clinically used therapy for LEMS, restored firing toward control IgG-treated levels (n=3), demonstrating pharmacologic rescue of IgG-induced functional deficits. qPCR analysis revealed compensatory transcriptional remodeling of presynaptic vesicle and postsynaptic acetylcholine receptor-clustering pathways, with increased expression of SV2B, SYN1, DOK7, RAPSN, and CHRNA1.Together, these findings establish a human NMJ organoid model that recapitulates molecular, structural, transcriptional, and functional features of LEMS using patient-derived IgG. This platform reduces reliance on large-volume passive-transfer animal models and provides a human-relevant system to investigate presynaptic calcium channel dysregulation, adaptive NMJ remodeling, and therapeutic rescue strategies for autoimmune NMJ disease.

Disclosures: C. Aguayo: None. **P.M. McNutt:** None.

Poster

PSTR266: Other Neuromuscular Diseases

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR266.14/Y17

Topic: C.06. Neuromuscular Diseases

Support: DTRA Grant #: HDTRA1-22-1-0029

Title: Broad-spectrum potential of 3,4-DAP in botulism across multiple serotypes

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Abstract: Despite the severe and often life-threatening paralysis caused by botulinum neurotoxins (BoNTs), there is no FDA-approved treatment to reverse botulism symptoms. Of the eight BoNT serotypes (A-G and X), serotypes A, B, C, and E are most frequently associated with human disease. All BoNTs cleave soluble NSF attachment protein receptor (SNARE) proteins required for calcium-evoked synaptic vesicle (SV) fusion, producing synaptic blockade and flaccid muscle paralysis. We previously demonstrated that the FDA-approved Kv channel

inhibitor 3,4-diaminopyridine (3,4-DAP) reverses paralysis in BoNT/A-poisoned rodent neuromuscular junctions through two mechanisms: increasing quantal content via enhanced release probability and productively re-engaging BoNT/A-cleaved SNAREs in release complexes. Here, we evaluate 3,4-DAP as a reversal agent for paralysis caused by BoNT serotypes E, C, and B in rodent models of botulism. Because respiratory collapse is the primary clinical driver of mortality in systemic botulism, we assessed ventilatory function using unrestrained whole-body plethysmography (UWBP) in mice challenged with different BoNT serotypes. A single 2 mg/kg dose of 3,4-DAP elicited significant peak improvements in minute volume (MV) of 550.9% (SE: 0.50%) in BoNT/E-challenged mice, 240.0% (0.20%) in BoNT/C, and 111.6% (0.09%) in BoNT/B, with no improvement observed in vehicle controls, and a lower 3,4-DAP dose (0.25 mg/kg) produced smaller but significant MV increases in BoNT/E- and BoNT/C-challenged mice, consistent with a dose-response relationship. Given the strong ventilatory rescue in mice, we next evaluated survival in rats, which require continuous infusion to maintain therapeutic plasma levels due to the short half-life of 3,4-DAP; rats challenged with lethal doses of BoNT/E or BoNT/C and continuously infused with 3,4-DAP (1.5 mg/kg·h) via subcutaneous catheter showed modest survival benefits compared to vehicle controls, with no improvement in survival rate but a significant prolongation in time to death for serotype E ($p = 0.01$) and not C ($p = 0.22$). To reconcile these findings, we assessed ventilatory responses in rats challenged with BoNT/E or BoNT/C and treated with 2 mg/kg subcutaneous 3,4-DAP, which produced peak MV improvements of 180.9% (0.3%) and 127.4% (0.1%), respectively. Collectively, these data show that 3,4-DAP reverses respiratory weakness across all tested BoNT serotypes, but only in BoNT/A does this enhancement reach the physiological threshold required to prevent respiratory arrest at lethal challenge doses, revealing a serotype-specific limit to pharmacological rescue.

Disclosures: W.T. McClintic: None. **P.M. McNutt:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.01/Y18

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

Support: NIH Grant R21-AG087039-01

Title: Mechanistic Timeline and Sex Difference in Sepsis Development

Authors: *L. WAGNER[1], Q. VO[2], J. HOLT[6], I. ALONSO DIAZ[3], D. NACIONALES[4], P. EFRON[4], P. CHAKRABARTY[2], G. CASADESUS[5];
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Abstract: Sepsis has been increasingly associated with cognitive deficits and dementia risk among survivors long-term. Blood-brain-barrier (BBB) damage followed by peripheral infiltration of pro-inflammatory molecules and immune cells drives neuroinflammation within the central nervous system (CNS) that can lead to cognitive decline and Alzheimer's Disease and related dementias (ADRD)-like features. Notably, these features may be sexually dimorphic, with worse cognitive outcomes post-sepsis in males. However, whether this pathological mechanism underlies CNS dysfunction in a clinically relevant model of sepsis such as the cecum ligation and puncture with daily chronic stress (CLP + DCS) model or whether these changes exhibit a sexual dimorphic pattern is unknown. To address this question, we used a $CX3CR1^{GFP}/CCR2^{RFP}$ double reporter mouse to track, neuroinflammatory, peripheral infiltration, BBB integrity, and microglial changes across time, as well cognitive changes using the Morris Water Maze (MWM) task. We also used nanostring to identify transcriptomic changes in early sepsis. We observed that in this model, infiltration of RFP+ monocytes, and pro-inflammatory cytokine transcription, preceded microglial activation. Notably, we observed cognitive deficits to occur only at the long-term post sepsis. Nanostring analysis also revealed sex differences in genes related to neuronal recovery. Together, our data indicates that peripheral infiltration occurs in translationally relevant models of sepsis and may drive a pathogenic mechanistic cascade leading to long-term cognitive deficits after sepsis recovery.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.02/Y19

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

Support: NIH Grant R25 AG076396
NIH Grant 1R21-AG087039-01

Title: Analysis of Neuronal Health Markers in Long-Term Post Sepsis Recovery

Authors: *S. LOUIDORT[1], L. WAGNER[2], J. HOLT[3], D. NACIONALES[1], P. CHAKRABARTY[3], P. EFRON[4], G. CASADESUS[2];
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Abstract: Several sepsis survivors experience long-term cognitive decline and are at increased risk of developing dementia, but the molecular drivers of these observations remain unclear. In our sepsis model, cecum ligation, and puncture (CLP)+stress, mice exhibited difficulty unlearning a behavioral task, indicating a possible decline in cognitive flexibility, a function primarily mediated by the prefrontal cortex (PFC). Initial analyses focused on hippocampal neuronal markers at 1 month (no cognitive deficits) and 4 months post-insult (cognitive deficits)

reveal selective changes in synaptic proteins (synaptophysin and spinophilin) that do fully temporally align with the observed cognitive deficits. Thus, because of the key role of the PFC in cognitive flexibility, we determined whether synaptic or signaling alterations in this region better align with the behavioral impairments. Ongoing experiments also include quantitative PCR to assess whether transcriptional regulation parallels protein-level expression across brain regions as previously observed in the hippocampus. This work aims to identify whether PFC-specific synaptic protein dysregulation contributes to post-sepsis cognitive impairment and to elucidate molecular pathways that may underlie long-term neurocognitive risk in sepsis survivors.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.03/Y20

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

Support: GRF Grant GR1000111
NIH Grant GR0533553

Title: The phosphatidylserine receptor Cd300f regulates monocyte-derived macrophage migration and phagocytosis in response to neurodegenerative stimuli

Authors: *R. YARCUSKO[1], A. MUKWAYA[1], H. VENKAT[1], Y. ZHANG[1], Z. YIN[2], G. BALDWIN[1], A. LENNIKOV[3], M. MARGETA[1];
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Abstract: Glaucoma, the leading cause of irreversible blindness, is characterized by loss of retinal ganglion cells (RGCs). Prior work has implicated neuroinflammation in glaucoma pathophysiology, in part governed by interactions between RGCs and activated myeloid cells such as microglia and macrophages. However, while targeting neuroinflammatory pathways may be a promising neuroprotective approach, the mechanisms of myeloid cell-mediated neurodegeneration remain poorly understood. Cd300f is a phosphatidylserine receptor expressed in myeloid cells that recognizes damaged or apoptotic cells and is upregulated in mouse models of glaucoma. Our preliminary data have shown that *Cd300f*$^{-/-}$ mice are protected from glaucomatous RGC loss, suggesting a critical role for Cd300f in neurodegenerative pathophysiology. To understand the role of Cd300f in glaucoma, we used a suite of assays to probe its function in myeloid cells. We first explored microglia-specific knockout of *Cd300f* in an *in vivo* mouse microbead glaucoma model and found no protective effect, suggesting that Cd300f affects glaucomatous neurodegeneration primarily through monocyte-derived macrophages. Thus, we cultured bone marrow-derived macrophages from *Cd300f*$^{-/-}$ and control

mice to explore their *in vitro* response to neurodegenerative stimuli. To assess migratory ability, we quantified macrophage migration through a porous membrane towards a dead neuron stimulus using immunocytochemistry. To quantify phagocytic ability, we seeded macrophages with apoptotic neurons and recorded phagocytosis with time-lapse imaging. We found that *Cd300f*$^{-/-}$ macrophages are less migratory and less phagocytic than control macrophages. Altogether, these results suggest a multifaceted role of Cd300f in glaucomatous neurodegeneration whereby Cd300f promotes monocyte-derived macrophage migration towards apoptotic RGCs, as well as their phagocytic capacity in a neurodegenerative retinal microenvironment.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.04/Y21

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

Support: Colgate University Research Council
Colgate University start-up awards

Title: Differential regulation of hypothalamic cytokine expression and microglia activation with onset of sickness behavior

Authors: M. TESOVIC, S. HASSAN, *A. NIRAULA;
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Abstract: Poly I:C is a double-stranded RNA used as a viral mimetic to study the immune response to infection. The sickness response following poly I:C administration is characterized by anorexia, thermoregulation, and reduced locomotion. The brain-body interactions that mediate the phenotypic presentation of sickness are still underexplored. This study aims to elucidate the neuroimmune response to a peripheral viral immune challenge and examine the brain region-specific molecular mechanisms underlying sickness. 8-12 week old male C57BL/6 mice were administered poly I:C or saline intraperitoneally. Poly I:C mice were divided into two groups with tissue collection at 24 hours post-injection (hpi) or 48hpi. Before sacrifice, physiological and behavioral measurements were recorded at several timepoints to assess the progression of sickness and recovery. Immunofluorescence labeling was used to examine microglia activation (Iba-1), neurovascular activation (ICAM-1), dopaminergic neurons (tyrosine hydroxylase), and neuronal activation (c-fos). Cytokine analysis was performed using RT-qPCR. To examine regional differences in the neuroimmune response, data were collected from the hypothalamus, hippocampus, and hindbrain. One-way ANOVA with post hoc pairwise comparisons were used for statistical analysis. Upon i.p. injections, poly I:C mice had

significantly reduced food intake and decreased relative body weight at 24hpi, which was completely recovered by 48hpi. Microglia activation in the arcuate nucleus was significant at 24hpi and reversed by 48hpi in the Poly I:C mice. In contrast, I-CAM1 expression showed a statistical trend towards an increase at 24 hpi, which was maintained at 48 hpi. Similarly, TNFα mRNA levels in the hypothalamus were elevated at 24 hpi and maintained at 48hpi. Preliminary examination of the neuronal response revealed no difference in the activation of the arcuate nucleus dopaminergic neurons with poly I:C. However, there was a reduction in arcuate nucleus tyrosine hydroxylase expression between 24 hpi and 48 hpi. Taken together, poly I:C triggered a robust sickness response and activation of the arcuate nucleus microglia, both of which were reversed by 48 hours. Restoration of food intake correlated with reduced tyrosine hydroxylase expression at 48 hours. Recovery from sickness occurred independent of TNFα expression. Ongoing work is focused on additional cytokines altered by poly I:C treatment and the neuroimmune mechanisms regulating dopaminergic signaling in the arcuate nucleus during sickness.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.05/Y22

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

Support: TARCC 23-476441
HT9425-25-1-0038

Title: Short-term Effects Of Circadian Rhythm Dysregulation On The Immune System

Authors: *H. L. SMITH[1], J. REYES[5], C. HARPER[2], E. IGLESIAS[2], A. XIN[3], E. TRAN[3], M. JACKSON[6], J. M. IANNUCCI[6], M. NEWELL ROGERS[7], D. J. EARNEST[8], K. M. SOUZA[4]; [1]Texas A&M Univ., Bryan, TX; [2]Texas A&M Univ., College Station, TX; [3]Neurosci. and Exptl. Therapeut., [4]NExT, Texas A&M Univ., Bryan, TX; [5]Texas A&M Univ. Hlth. Sci. Ctr. - Col. of Med., Bryan, TX; [6]Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; [7]Surgery, Texas A&M Hlth. Sci. Ctr. Col. of Medicin, Temple, TX; [8]Neurosci & Exp. Therapeut., Texas A&M Hlth. Sci. Ctr. Col. of Medicin, Bryan, TX

Abstract: Background: Disturbances of the sleep-wake cycle and other circadian rhythms typically precede the age-related deficits in learning and memory, suggesting that these alterations in circadian timekeeping may contribute to the progressive cognitive decline during aging and in Alzheimer's disease and related dementias (AD/ADRDs). However, the extent to which early circadian rhythm dysregulation affects cognitive aging remain unclear. Particularly, it is still unknown what specific molecular and cellular mechanisms link circadian function to age-related neurodegeneration.**Methods:** Building on our previous findings of long-term B cell

expansion following an established light-dark (LD) cycle-shifting paradigm, we examined whether controlled circadian disruption (CCD) acutely affects the adaptive and innate immune system and cognitive performance. Young C57BL/6J mice (3-6 months old) were subjected to an 80-day CCD paradigm consisting of repeated 12-hour advances of the LD cycle every 5 days. One week after the final shift, cognitive performance was evaluated using the Barnes maze, along with additional behavioral assessments including the three-chamber sociability, open field, and novel object/location recognition tests. Immune cell activation was also analyzed in peripheral tissues and the brain.**Results:** Our results show that CCD induces significant acute alterations in the adaptive immune system of young mice. While cognitive and social behavioral changes were present, they were relatively mild.**Conclusion:** These findings suggest that circadian desynchronization rapidly impacts immune function, potentially setting the stage for long-term immune and cognitive consequences associated with sleep and circadian rhythm disturbances.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.06/Y23

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

Support: NIH R21NS108771
William C Roland Parkinson's Disease Research Fund

Title: Distinct peripheral immune populations contribute to LRRK2-dependent Parkinsonian pathology following H1N1 influenza infection

Authors: *S. GUNASEKARA[1], R. J. SMEYNE[2], E. KOZINA[1];
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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and significant immune dysregulation. Increasing evidence suggests that aberrant peripheral immune responses contribute to PD pathogenesis through gene-environment interactions. The G2019S missense mutation in leucine-rich repeat kinase 2 (LRRK2), the most common genetic cause of familial PD and a contributor to sporadic PD, enhances kinase activity which may drive abnormal inflammatory signaling linked to neurodegeneration. Our previous studies demonstrated that non-neurotropic H1N1 influenza infection, induces SNpc DA neuron loss and prolonged neuroinflammation in G2019S mice without direct viral neuroinvasion. Given the broad expression of LRRK2 in peripheral immune populations and the absence of detectable

viral proteins or immune-cell infiltration in the brain, we hypothesize that specific circulating immune cell subsets mediate the neurodegenerative phenotype induced by peripheral infection. Hence, using lineage-specific Cre/loxP technology, we crossed G2019S-KI floxed mice with CD19-Cre, CD4-Cre, CD8-Cre, Mrp8-Cre, and CX3CR1-Cre drivers to selectively excise mutant LRRK2 from B cells, T cells, neutrophils, and monocytes/macrophages, respectively. Mice (n=10) were intranasally infected with influenza (H1N1, A/CA/04/2009) and analyzed at 0, 2, 4, 7, 30, and 60 days post infection using stereological quantification of SNpc DA neuron loss, flow cytometric immunophenotyping, transcriptomic profiling, and multiplex analysis of both peripheral and brain immune compartments. Selective excision of mutant LRRK2 in CD19+ and CX3CR1+ cell populations significantly rescued SNpc DA neuron loss and attenuated inflammatory pathology following infection compared to infected G2019S controls, whereas deletion in CD4+, CD8+, and Mrp8+ populations produced no neuropathological rescue. Flow cytometric analyses demonstrated lineage-dependent alterations in peripheral immune activation and immune-cell composition following infection, while preliminary transcriptomic and cytokine analyses revealed distinct inflammatory and antiviral signaling signatures associated with protective versus non-protective immune populations. Together, these findings identify discrete peripheral immune populations as key mediators of LRRK2-dependent inflammation-induced neurodegeneration, supporting a role for dysregulated peripheral immunity in PD pathogenesis and highlighting potential biomarkers and immunomodulatory therapeutic targets for PD.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.07/Y24

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

Support: R00 DA044838 (DWW)
R01 DA052859 (DWW)
U01 DA058527 (DWW)

Title: Peripheral immune cells contribute to chronic neuroinflammation by migrating across the blood brain barrier in a heterogenous and donor-dependent manner

Authors: *R. COLÓN-ORTIZ[1], A. MERCADO[2], S. KNERLER[3], J. DIETRICH[3], A. PRICE[3], A. ELLISON[3], L. MAMUN[3], D. W. WILLIAMS[3];
[1]Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Med. Scientist Training Program MD-PhD, Stanford Univ., Stanford, CA; [3]Pharmacol. and Chem. Biol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Neuroinflammation is a hallmark of neurological disease and neurodegenerative disorders, although large inter-human variability in presentation, severity, and progression has

been widely documented. While central nervous system (CNS)-resident immune cells are best characterized, emerging studies highlight the peripheral immune system as a key contributor to chronic neuroinflammation. At baseline conditions, the blood brain barrier (BBB) regulates transport from circulating blood into the brain to maintain CNS homeostasis. However, peripheral blood mononuclear cells (PBMC), including monocytes and T-cells, are increasingly recruited across the BBB by chemotaxis during CNS pathology. Interestingly, expression of cell-surface markers that facilitate BBB migration and inflammatory responses are not uniform across PBMC populations or even within the same cell subsets, which could differentially prime specific PBMC to traffic across the BBB. We hypothesized that PBMC subsets with canonically established pro-inflammatory phenotypes, such as CD14+CD16+ monocytes, are preferentially recruited across the BBB under inflammatory conditions. To address this, PBMC were isolated from 100 healthy donors. We used our novel tricellular in vitro model of the BBB consisting of primary human brain microvascular endothelial cells, astrocytes, and pericytes cocultured on a transwell insert. PBMC were added to the apical portion of the insert and allowed to migrate for 24 hours in response to CCL2, CXCL12, or vehicle control. Transmigrated cells were collected from the basolateral portion and analyzed by flow cytometry. Surprisingly, we found large inter-donor variability in general monocyte migration, not only CD14+CD16+ activated cells, across all conditions. T-cell migration also varied across donors, though this heterogeneity was specific to CXCL12 and occurred to a lesser extent than it did for monocytes. Expression of the cell-surface migration markers ALCAM, JAM-A, PECAM, and CCR2 was also elevated in a donor-specific manner in monocyte populations. Our findings suggest that heterogeneous and donor-dependent PBMC migration across the BBB may represent an underappreciated source of inter-human variability in neuroinflammatory susceptibility and progression during CNS pathology.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.08/Y25

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

Support: Howard Hughes Medical Institute Hanna H. Gray Fellowship

Title: Sequential pathogen exposure normalizes the brain neuroimmune microenvironment and reveals a tissue-resident memory CD8 T cell-microglia axis shaping adult neurogenesis

Authors: *C. E. FAIN[1,2], M. R. MIX[3], L. P. EPPING[2], S. KANNAN[3], M. HEIDARIAN[2], E. ESCUE[4], V. P. BADOVINAC[2], J. T. HARTY[2];
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Abstract: T cells are increasingly recognized as long-term residents of the adult brain, where they accumulate with age and exhibit regional diversity. However, the functional consequences of brain T cell residency on CNS microenvironments are not well-understood, particularly in non-aged populations. Conventionally used, young adult Specific Pathogen Free (SPF) mice, exhibit low numbers of T cells in the brain compared to young adult humans, limiting translational relevance. In this work we utilize our Specific Pathogen Experienced (SPExp) mouse model, in which prior peripheral microbial exposures lead to significant enrichment of tissue-resident memory (Trm) T cells in the brain, generating a neuroimmune state more closely resembling adult humans. Using this model we recently demonstrated that the presence of resident T cells in the brain influences seizure outcomes in young mice. Here we combined spectral flow cytometry, single-cell RNA sequencing, tissue clearing, behavioral analyses, intravital imaging and blockade strategies to define how CD8 Trm impact brain microenvironment. At immune memory timepoints following peripheral pathogen exposures, SPExp mice exhibited CD8 Trm localization near neurogenic niches in the brain. Sholl analysis of microglia in the vicinity of these neurogenic niche CD8s displayed a more activated phenotype. Intravital imaging demonstrated that CD8 Trm are motile and form sustained contacts with microglia *in vivo,* corresponding to the changes in activation state. RNAseq identified robust CD8 T cell-dependent transcriptional changes in microglia. Differential expression revealed distinct primed and senescence-associated microglial phenotypes enriched for interferon-signaling, metabolic stress adaptation, and immune surveillance genes and down regulated neuronal support and signaling genes; with reversal of this upon CD8 T cell depletion. Additionally, KEGG/GO analyses suggest induced microglial states downregulate support for neuronal development. Flow and imaging data found neural stem cells (NSCs) were increased in the niches, but proliferation was abrogated. Proliferation of NSCs was restored after CD8 depletion. Together, these findings identify CD8 Trm as key regulators of microglial state and neurogenesic capacity in the brain, establishing a new paradigm for adaptive immune regulation of brain function at homeostasis.

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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.09/Web Only

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

Support: NIH Grant GM146257
NIH Director's Transformative Research Award for Accelerating Leading-edge Science in ALS (ALS2) Initiative
South Carolina SmartState Endowment for Economic Growth

Title: Gut Inflammation Induces Brain Tau Hyperphosphorylation and Loosens Blood-Brain Barrier in Mice

Authors: S. WOZNY, M. S. KALSOW, R. TATUM, Y.-H. CHEN, *Q. LU;
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Abstract: Claudin-7 is a tight junction protein involved in maintaining epithelial barrier integrity and regulating inflammatory homeostasis. Deletion of claudin-7 in mice causes severe intestinal inflammation and activates inflammatory signaling pathways. However, its potential role in neuroinflammation and neurodegenerative pathology is unknown. This study investigated whether inducible, intestinal-specific claudin-7 knockout in mice influences markers associated with neuroinflammation and Alzheimer's disease (AD) pathology. Wild-type (WT) and conditional claudin-7 KO mice (cKO) were treated with Tamoxifen to induce claudin-7 deletion specific in intestines. Brain tissues from WT and cKO mice were isolated, processed, and then analyzed using immunofluorescent staining and Western blot analysis. Markers examined included amyloid-beta (Aβ), phosphorylated tau (p-tau), MAP-2, GFAP, Claudin-5, and microglial marker Iba1 in cortex as well as within the dentate gyrus (DG), CA1 and CA3 regions of the hippocampus in brain. Immunofluorescent imaging was performed using a Zeiss Axio Observer 7 microscope, and image analysis was conducted using ImageJ software. Our results demonstrated an increased AD-like hyperphosphorylation of tau and a reduced claudin-5 expression in cKO brains compared to WT brains by both immunofluorescent staining and Western blot analysis. While overall brain Iba1 expression level was reduced on Western blot, its expression in the hippocampus was increased. On the other hand, there was no change in MAP2 expression on Western blot although its expression in the hippocampus was reduced in cKO mice. GFAP and amyloid-beta (Aβ) signals were variable among individual WT and cKO mouse pairs. Hyperphosphorylated tau is a hallmark of AD pathology and contributes to neurofibrillary tangle and subsequently neuronal dysfunction. Reduced claudin-5 expression is consistent with the blood-brain barrier loosening due to gut claudin-7 deficiency-induced inflammation. These findings suggest that intestinal-specific Claudin-7 loss may contribute to neuroinflammatory signaling and AD-related pathological changes, potentially linking intestinal barrier dysfunction to neurodegenerative disease progression.

Disclosures: S. Wozny: None. **M.S. Kalsow:** None. **R. Tatum:** None. **Y. Chen:** None. **Q. Lu:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.10/Y26

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

Support: NRSA F32 Fellowship MH120966-01
NIMH R01 MH094527

John Nambu Memorial Summer REU
FAU OURI award
ASCEND Program Fellowship

Title: Peripheral inflammation limits serotonin signaling capacity via serotonergic IL-1R1 by reducing neuronal excitability and enhancing clearance

Authors: *P. A. GAJEWSKI[1], H. IWAMOTO[2], A. TILLMAN[3], Z. FILLIBEN[2], N. L. BAGANZ[2], M. J. ROBSON[4], M. ZAPATA[2], N. QUAN[2], R. D. BLAKELY[2];
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Abstract: Evidence indicates that neuropsychiatric disorders, including major depressive disorder and schizophrenia, are frequently accompanied by dysregulation of immune signaling pathways. The substantial comorbidity between mood disorders and chronic inflammatory diseases suggests that shared neuroimmune mechanisms may contribute to disease pathophysiology. Previous work from our laboratory demonstrated that activation of the peripheral innate immune system in mice increases serotonin (5-HT) clearance in vivo and promotes anxiety- and despair-like behaviors via a mechanism requiring serotonergic p38α MAPK. However, cellular and circuit-level processes linking peripheral immune activation to altered serotonergic neurotransmission remain incompletely understood. Given the central role of dorsal raphe nucleus 5-HT-producing neurons in the regulation of affective behaviors, we investigated how proinflammatory signaling influences their function. Whole-cell patch-clamp recordings revealed that the cytokine interleukin-1β (IL-1β) directly suppresses 5-HT neuronal excitability through activation of the IL-1 receptor type 1 (IL-1R1) and downstream p38α MAPK signaling. Consistent with the effects of systemic lipopolysaccharide (LPS) administration, local delivery of IL-1β into the hippocampus produced a rapid enhancement of 5-HT clearance measured by in vivo chronoamperometry. We found that tumor necrosis factor-α (TNFα) similarly decreases 5-HT neuron excitability. Immunocytochemical analyses demonstrated heterogeneous IL-1R1 expression among 5-HT neurons and identified a requirement for this receptor in LPS-induced suppression of serotonergic neuronal activity, as assessed by cFos expression. Collectively, these findings define molecular and circuit mechanisms through which peripheral innate immune activation modifies central serotonergic function. The results highlight a critical role for serotonergic IL-1R1 signaling in mediating the effects of inflammatory cytokines on 5-HT systems and suggest that immune-driven reductions in serotonergic excitability, together with enhanced 5-HT clearance, contribute to neurophysiological and behavioral adaptations associated with inflammation. Current studies are exploring omics technologies to define IL-1R1 dependent pathways that may be suitable for medication development in disorders that feature 5-HT dysfunction.

Disclosures: P.A. Gajewski: None. **H. Iwamoto:** None. **A. Tillman:** None. **Z. Filliben:** None. **N.L. Baganz:** None. **M.J. Robson:** None. **M. Zapata:** None. **N. Quan:** None. **R.D. Blakely:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.11/Y27

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

Support: Hong Kong PhD Fellowship Scheme
HKU Presidential Scholarship
Bingei and L & T Charitable Foundation Professorship in Dementia Research

Title: Investigating the consequences of metabolic reprogramming on neuroimmune responses after systemic inflammation

Authors: *K. OH[1,2,3], J. YOO[3], G. T. C. WONG[1], R. CHANG[2];
[1]Dept. of Anaesthesiology, Sch. of Clin. Medicine, LKS faculty of Med., [2]Lab. of Neurodegenerative Diseases, Sch. of Biomed. Sciences, LKS Fac. of Med., The Univ. of Hong Kong, Hong Kong, Hong Kong; [3]Optical Imaging Group for Translational Medicine, Dept. of Hlth. Technol. and Informatics, The Hong Kong Polytechnic Univ., Hong Kong, Hong Kong

Abstract: Immune crosstalk between body and brain is increasingly being recognized. Sterile and non-sterile inflammation activates immune cells in the body leading to systemic inflammation. Systemic inflammation can further induce neuroimmune responses via various mediators. This study investigated whether systemic inflammation could induce neuroimmune responses in young adult mice and whether these neuroimmune responses persist after the systemic inflammation has been resolved. Sterile inflammation was induced by a laparotomy performed under sevoflurane. Non-sterile inflammation was induced by bacterial endotoxin challenges. A second episode of systemic inflammation was induced 28 days after the first to assess the differential neuroimmune responses between first and second challenges. The neuroimmune responses were evaluated by investigating the activation of microglia. Microglia activation in the hippocampus persisted until at least day 14 when systemic inflammatory has subsided. The hippocampus displayed enhanced glycolysis and attenuated TCA cycle after the first or second challenges. Afterwards, it was hypothesized that the metabolic changes in persistent neuroimmune responses might be implicated in mitochondrial damage. To verify this hypothesis, recombinant adeno-associated virus was designed and injected into the lateral ventricle of the mice to detect mitochondrial damage (mitophagy) in microglia. The mitochondrial and DNA damage were detected in the hippocampus indicating that the metabolic changes were associated with mitochondrial damage and dysfunction. To further investigate the effects of metabolic alteration in microglia, other recombinant adeno-associated viruses were designed to downregulate glycolytic enzymes, phosphofructokinases 1/2, respectively, in microglia. Consequently, it significantly reduced mitochondrial and DNA damage in the hippocampus after systemic challenges. In addition, the intensity of homeostatic microglia has significantly increased. This study advanced our understanding of the metabolic changes and nuclear damage in the neuroimmune responses followed by mitochondrial damage. Taken together, downregulation of enhanced glycolysis in microglia could be a potent therapeutic strategy to prevent neuronal damage after systemic inflammation.

Disclosures: K. Oh: None. **J. Yoo:** None. **G.T.C. Wong:** None. **R. Chang:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.12/Y28

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

Support: NIH Grant 5R01NS126981

Title: Prenatal microglia priming by prostaglandin pathway activation leads to lifelong blood-brain barrier breakdown and neuroinflammation

Authors: *Y. LIU;
USC, Los Angeles, CA

Abstract: Maternal immune activation (MIA) during pregnancy is a known risk factor for neurodevelopmental disorders (NDDs). MIA induces lifelong neuropathology and behavioral alterations in mouse offspring. Our previous work demonstrated that MIA disrupts blood-brain barrier (BBB) development and function and induces persistent microglial activation across the offspring lifespan. Given that vascular dysfunction and neuroinflammation contribute to NDD pathology, MIA-induced BBB disruption may play a causal role in disease etiology. However, the mechanisms driving this disruption and the role of microglia remain unclear.We use poly(I:C), a viral mimetic administered to pregnant mice, to induce MIA at gestational day (GD)13. MIA activates the cyclooxygenase-2 (COX2)-prostaglandin E2 (PGE2) pathway in fetal microglia, and this activation persists postnatally. We hypothesize that COX2 activation primes fetal microglia, altering their immune phenotype and impairing microglia-BBB interactions throughout life. Using primary fetal microglial cultures, we are investigating how COX2-PGE2 pathway stimulation affects immune activation status and macrophagic function. Microglia were isolated using magnetic-associated cell sorting (MACS) and cultured in pericyte-conditioned medium yielding 80% +/- 10% purity. MACS-isolated fetal microglia treated with PGE2 showed increased COX2 and decreased CD68 immunofluorescence intensity. Results suggests that MACS isolation induces a highly activated microglial state where PGE2 functions as an anti-inflammatory mediator.To determine whether COX2-activated microglia contribute to sustained blood-brain barrier disruption in postnatal offspring, we developed a microglial depletion and repopulation strategy using the CSF1R inhibitor PLX5622 in diet for three weeks from postnatal day (PD)21 to 42. Depletion efficiency is strain dependent, as PLX5622 treatment depletes 90% +/- 10% and 60% +/- 10% of microglia in the cortex (motor and somatosensory) in C57 and CD1 mice. After PLX5622 cessation, newly generated microglia repopulated the brain within three weeks. Importantly, Poly(I:C)-mediated microglial overactivation and impaired BBB pericyte coverage of endothelial cells in the cortex were rescued after microglial depletion-repopulation. These results indicate that primed, activated microglia play a causal role in maintaining Poly(I:C)-induced BBB breakdown across the offspring lifespan. The results will provide important insights for identifying the developmental etiology and molecular mechanisms of vascular dysfunction and neuroinflammation in NDDs.

Disclosures: Y. Liu: None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.13/Y29

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

Support: NIH Grant R01AA030469
NIH Grant T32AA025606

Title: Ibudilast dose-dependently alters poly I:C-induced fever and ethanol-induced hypothermia

Authors: *S. TRAPP, T. DEAK;
Binghamton Univ., Binghamton, NY

Abstract: Ibudilast is a PDE4 inhibitor that has recently emerged as a potential therapeutic for alcohol use disorder. Since neuroimmune activation contributes to thermoregulatory responses induced by immune challenge, the goal of the present work was to investigate the dose-dependent effects of ibudilast treatment on fever sensitivity and ethanol-induced hypothermia. Adult female Sprague Dawley rats received an intraperitoneal (i.p.) injection of either saline or a drug challenge in 3 distinct phases separated by 5-7 days. Before each drug challenge, rats were given a subcutaneous (s.c.) injection of either 0, 3, or 9 mg/kg ibudilast (n=8-10 per group; N=50). To assess fever and hypothermia, body temperatures were recorded in 30 minute intervals 2 hr before drug challenge and for 4-8 hr after drug challenge. In phase 1, rats were challenged with saline or 12 mg/kg polyinosinic:polycytidylic acid (poly I:C). Poly I:C-injected animals treated with 9 mg/kg ibudilast had significantly lower body temperatures compared to vehicle from 2-4 hours after the poly I:C challenge. While there were no differences in peak fever response and maximum change from baseline between ibudilast dose groups, latency to peak fever was longer in poly I:C-injected animals treated with 9 mg/kg ibudilast, indicating a delayed fever response. In phase 2, rats received either saline or 2 g/kg ethanol. Ethanol-injected animals that received 9 mg/kg ibudilast had significantly lower body temperature relative to controls from 0.5-4 hours post injection. Similarly, peak hypothermic response, maximum change from baseline, and latency to peak hypothermic response was greater in the ethanol-injected animals treated with 9 mg/kg ibudilast compared to vehicle treated animals. These findings showed that 9 mg/kg ibudilast exacerbated ethanol-induced hypothermia. In phase 3, rats were challenged with saline or 100 µg/kg lipopolysaccharide (LPS). LPS-injected rats treated with 9 mg/kg ibudilast had significantly lower body temperatures compared to controls from 2-5.5 hours post LPS challenge. Yet, there was no effect of ibudilast dose on peak fever response, maximum change from baseline, and latency to peak fever in LPS-treated animals. Across all 3 phases, 9 mg/kg ibudilast consistently reduced body temperature post-injection, regardless of drug challenge. Together, these findings indicate that ibudilast delayed fever response to poly I:C, but not LPS, and exacerbated the hypothermic effects of ethanol in a dose-

dependent manner. These findings provide important insight into the divergent thermoregulatory mechanisms underlying ethanol-induced hypothermia and inflammatory challenges.

Disclosures: S. Trapp: None. **T. Deak:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.14/Y30

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

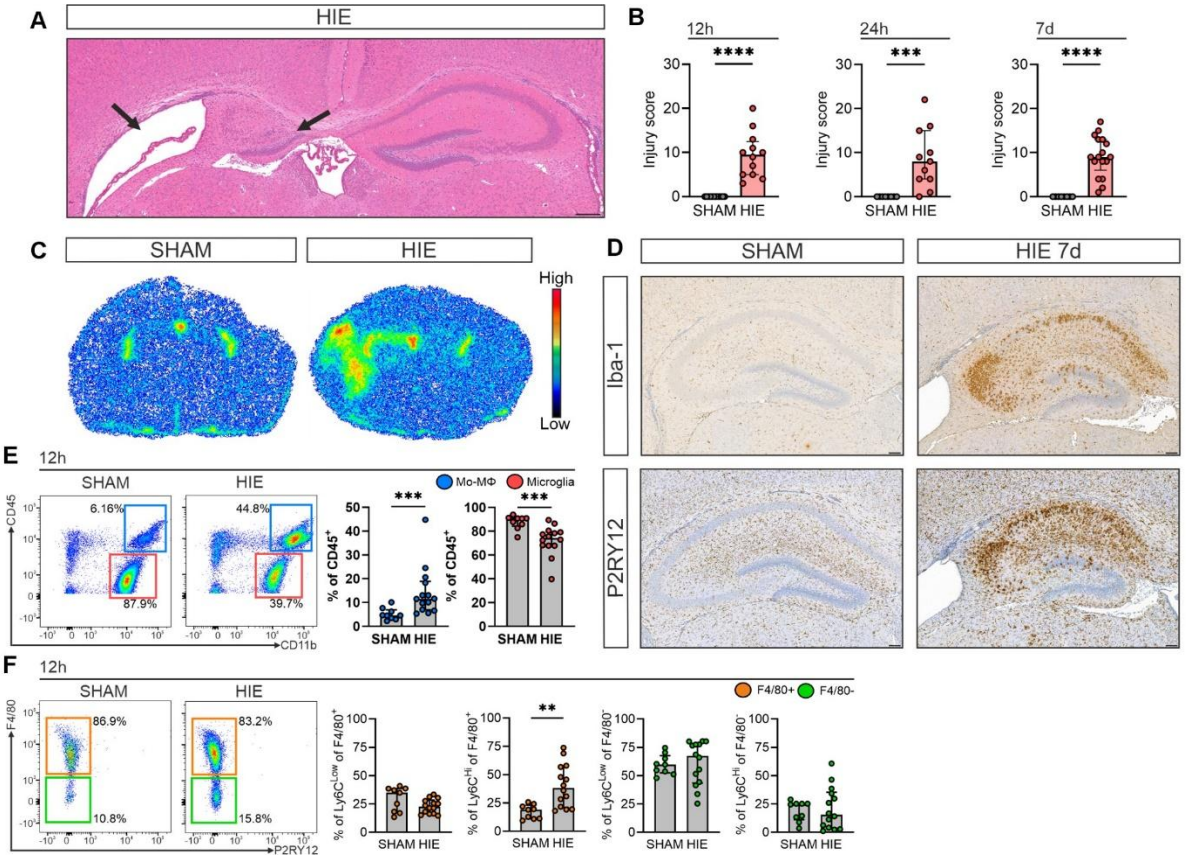
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Title: Immunophenotypic characterization and spatial localization of brain-resident and infiltrating myeloid cells in the mouse brain of neonatal hypoxic-ischemic encephalopathy

Authors: *H. NYKÄNEN[1,2,3], E. LOKKA[3,4], M. SALMI[1,3,5], T. GRÖNROOS[1,2], P. RANTAKARI[3,4], V. PARIKKA[1,2,3,6,7];
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Abstract: Neonatal hypoxic-ischemic encephalopathy (HIE) is a severe birth complication resulting from oxygen and glucose deprivation. In a triggered pathophysiological cascade, inflammation, excitotoxicity, and oxidative stress aggravate brain injury. In the acute phase, activated microglia and peripheral myeloid cells infiltrate affected brain regions. However, the kinetics of specific leukocyte populations in HIE remain poorly understood. Here, P9-P10 C57BL/6J mice of both sexes underwent unilateral common carotid artery ligation followed by systemic hypoxia (9% O_2, 60 min). A total of 212 mice from 41 independent litters were assigned to the sham-operated control (n=91) or HIE (n=121) group. AI-based histopathological analyses were performed 12h, 24h, and 7d post-hypoxia. Brain-resident and blood-derived myeloid cells were isolated from the ipsilateral hemisphere at the same time points and analyzed using spectral flow cytometry. In addition, changes in the brain cytokine profile were examined

using qPCR. We observed severe ipsilateral hippocampal atrophy and reactive amoeboid microglia densely localized to the ipsilateral hippocampus and deep thalamic regions (Fig. A-D). Myeloid cell influx peaked at 12h post-hypoxia, as reflected by increases in the frequencies of monocyte-derived macrophages (Fig. E, Mann-Whitney U p=0.0005) and neutrophils. In contrast, the frequency of microglia declined. Moreover, infiltrating monocytes started expressing the macrophage marker F4/80, with a prominent increase in the frequency of F4/80^{+}Ly6C^{Hi} cells at 12h post-hypoxia (Fig. F, Mann-Whitney U p=0.0020). Correspondingly, expression of activation markers CD86 and MHC-II increased considerably on microglia at 12h and 24h post-hypoxia. Overall, spectral flow cytometry revealed phenotypic alterations in brain-resident microglia and prominent infiltration and maturation of monocytes into activated monocyte-derived macrophages in the hypoxic-ischemic brain. Our data enhances the understanding of leukocyte subpopulations contributing to hypoxic-ischemic injury.



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Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.15/Y31

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

Support: FASI (Food Allergy Science Initiative)
Arizona Depatment of Health

Title: Food Allergy Induces Region-Specific Transcriptional Responses in the Brain

Authors: *C. WOODROW[1], B. COSTA LIMA[4], P. KHER[1], A. ROGINSKI[2], E. BORGES FLORSHEIM[3];
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Abstract: Food allergy has been shown to promote behavioral changes, such as allergen avoidance, suggesting that the central nervous system (CNS) is affected by allergen exposure in the gut. However, the molecular responses within specific brain regions during allergic inflammation remain poorly understood. Here, we examined transcriptional changes in the brains of allergic mice to determine whether food allergy alters inflammation pathways within the CNS.Using an established ovalbumin (OVA)-induced gut inflammation in female BALB/c mice, animals were sensitized with OVA and alum and later challenged by oral gavages. Control groups received alum alone during sensitization and also received oral OVA during challenges. Brain tissue from the frontal cortex, pons, hypothalamus, cerebellum, medulla, and hippocampus was collected upon dissection 24 hours after five allergen challenges. Transcriptional programs were analyzed by qPCR after RNA extraction. Gut allergic inflammation was confirmed by elevated serum IgE and IgG1 levels, Chloroacetate esterase (CAE) staining of the duodenum, and qPCR analysis of duodenum inflammatory markers.
At 24 hours post-challenge, the frontal cortex exhibited a general reduction in transcriptional activity. The transcription factors Sox10 and Cited4 were significantly downregulated in allergic mice compared to controls. Sox10 serves as a key regulator of oligodendrocyte development and myelin maintenance, whereas Cited4 acts as a transcriptional coactivator involved in multiple cellular pathways and is implicated in oligodendrocyte-related processes.
No significant differentially expressed genes were identified in the cerebellum, hypothalamus, or medulla. Further investigation is ongoing in the pons and hippocampus regions.
These findings suggest that gut allergic inflammation induces region-specific transcriptional responses in the brain, characterized by decreased expression of transcription factors critical for oligodendrocyte development and function in the frontal cortex, potentially contributing to behavioral changes beyond what has been previously shown. These results provide insight into potential neuroimmune mechanisms through which peripheral allergic inflammation may influence brain function and behavior.

Disclosures: C. Woodrow: None. **B. Costa Lima:** None. **P. Kher:** None. **A. Roginski:** None. **E. Borges Florsheim:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.16/Y32

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

Support: NIH/NIAID grant 1R01AI168563

Title: Allergen avoidance reverses cognitive deficits and neuropathological changes induced by allergen exposure in a mouse model of subclinical food allergy

Authors: *G. VERMA[1], K. NAGAMOTO-COMBS[2];
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Abstract: Individuals with subclinical food allergy tolerate offending allergens without overt physical or life-threatening symptoms. Using a mouse model of subclinical food allergy, we have previously demonstrated that chronic allergen consumption induces cognitive deficits, neuroinflammation, and cortical demyelination, particularly in males. Because allergen avoidance is the primary management strategy for food allergy, we investigated whether the removal of the dietary allergen could reverse these neuropathologies. Four weeks old male and female C57BL/6J mice were sensitized to a bovine whey allergen, β-lactoglobulin (BLG; Bos d 5), and subsequently fed a whey protein (WP)-containing diet for 2 weeks. Mice were then either maintained on the WP diet or switched to an allergen-free (CTL) diet for an additional 2 weeks. When behavioral performance and neuropathological changes were examined, BLG-sensitized mice that stayed on the WP diet showed cognitive deficits assessed by the novel object recognition test. The performance of BLG-sensitized mice on the CTL diet was equivalent to that of their sham-sensitized counterparts. BLG-sensitized male mice on the WP diet also showed increased numbers GFAP+ astrocytes, Iba1+ microglia, and CD45+ cells in the brain, suggesting persistent neuroinflammation with astrogliosis, microgliosis, and leukocyte infiltration, respectively. Because neuroinflammation is known to impair oligodendrocyte survival, maturation, and myelin maintenance, we immunohistochemically evaluated myelination status and oligodendrocytes. BLG-sensitized male mice on the additional 2 weeks of WP diet showed notably lower myelin-basic protein (MBP) levels compared to sham mice on the same diet. However, this difference was not apparent between sham and BLG-sensitized mice on the CTL diet, indicating that the allergen avoidance resulted in remyelination. Additionally, BLG-sensitized male mice, but not female mice, had reduced numbers of cortical Olig2+ cells regardless of diet, suggesting that the rate of oligodendrocyte maturation or turnover was slower in these mice. Together, these findings indicate that continued allergen consumption leads to persistent cognitive impairment associated with prolonged neuroinflammation, with males being more susceptible. Importantly, however, we found that these neuropathologies could be partly reverted by removing the allergen from the diet, highlighting the importance of allergen avoidance, even in individuals with a subclinical food allergy.

Disclosures: G. Verma: None. **K. Nagamoto-Combs:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.17/Z1

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

Support: JSPS KAKENHI Grant Number 25K19849

Title: Inflammatory responsiveness of microglia-like cells derived from peripheral blood monocytes is associated with postoperative pain in men.

Authors: *S. MATSUSHITA[1], Y. MATSUOKA[2], F. AMAYA[3];
[2]Anesthesiol., [1]Kyoto Prefectural Univ. of Med., Kyoto, Japan; [3]Kyoto Prefectural Univ. of Med., Kyoto-Shi, Japan

Abstract: Background: Microglia play a critical role in pain perception. Although microglial activation has been demonstrated in animal models of pain, the relationship between microglial activation and pain in humans remains unclear. In this study, we generated induced microglia-like cells (iMG cells) from peripheral blood monocytes and examined whether their inflammatory responsiveness was associated with postoperative pain in patients undergoing lung cancer surgery. Methods: This study included patients with lung cancer who underwent thoracic surgery. Peripheral blood samples were collected, monocytes were isolated, and iMG cells were generated under defined culture conditions. The iMG cells were stimulated with lipopolysaccharide (LPS), and TNF-α mRNA expression was quantified using real-time polymerase chain reaction. The change in TNF-α mRNA expression before and after LPS stimulation was used as an indicator of cellular responsiveness. Postoperative pain intensity was assessed using the Numerical Rating Scale (NRS; 0-10). Patients were classified into a severe pain group (maximum NRS score ≥5) and a mild pain group (maximum NRS score <4) based on the highest NRS score recorded during the first 3 postoperative days. The change in TNF-α mRNA expression was compared between the groups. This study was approved by the institutional ethics committee (Approval No. ERB-C-3605). Results: Of the 50 patients, 20 were classified into the severe pain group and 27 into the mild pain group. Among male patients, the LPS-induced increase in TNF-α mRNA expression in iMG cells was greater in the severe pain group than in the mild pain group. No significant association between iMG cell responsiveness and postoperative pain intensity was observed in female patients. Conclusions: Increased inflammatory responsiveness of patient-derived iMG cells was associated with severe postoperative pain in male patients undergoing lung cancer surgery. These findings suggest that microglial-like cellular responsiveness in peripheral blood-derived cells may reflect individual susceptibility to postoperative pain.

Disclosures: S. Matsushita: None. **Y. Matsuoka:** None. **F. Amaya:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.19/Z3

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

Support: National Institute of Neurological Disorders and Stroke Grant 1K99NS138490-01
National Institute of Neurological Disorders and Stroke Grant NS103212-09

Title: Brain-penetrant microglia-targeted mRNA lipid nanoparticles enhance T cell anti-glioma immunity

Authors: *Z. TIAN[1,2], F. JIN[3], M. MAYNES[3], M. PEDRA SEADY[3], J. MERIDEW[4], A. TAVALLAEI[6], A. HASSANI[5], A. J. JOHNSON[3];
[1]Mayo Clin., ROCHESTER, MN; [2]Neurosci. Dept., [3]Immunol., [4]DLMP, Mayo Clin., Rochester, MN; [5]Mayo Clin., rochester, MN; [6]Neurosci., Mayo Clin. Grad. Sch. of Biomed. Sci., Rochester, MN

Abstract: Glioblastoma (GBM) is the most aggressive primary brain tumor and remains incurable despite intensive therapy, in part due to its immunosuppressive tumor microenvironment (TME). The GBM TME showed ineffective cytotoxic T-cell responses, driven by inefficient tumor antigen presentation and limited T-cell infiltration. Microglia as dominant resident immune population in the brain and are enriched in GBM TME, positioning them as potential antigen-presenting cells capable of shaping anti-tumor immunity. However, the ability of microglia to present tumor antigens and activate $CD8^+$ T cells remain poorly understood, and tools to harness this function are lacking. To address this gap, we developed microglia-targeted lipid nanoparticles (LNPs) and hypothesized that delivery of tumor antigen-encoding mRNA to microglia would enable antigen expression and presentation, thereby priming antigen-specific T cells and promoting anti-tumor immune responses. We screened 96 LNP compositions of helper lipids and ionizable lipids and tested their efficacy for luciferase mRNA delivery to microglia. The LNP formulation selected for in-vivo safety and delivery efficacy was then coated with a microglia-targeting antibody and tested in vivo for Cre recombinase mRNA delivery in Ai9 reporter mice to identify LNP-targeted cells by flow cytometry. we confirmed enhanced mRNA delivery to $CD45^{mid}$ $TMEM119^+$ microglia with microglia-targeted LNPs (87.8%) compared with uncoated LNPs (2.9%) or non-targeting isotype IgG-coated LNPs (8.5%). The microglia-targeted LNPs were further evaluated for OVA mRNA delivery in murine GBM model GL261-OVA to assess its potential to enhance tumor-antigen-specific response.Tumor-bearing mice received either microglia-targeting OVA-mRNA LNPs or empty vehicle control through intrathecal injections. One-week post-injections, we used spectral flow cytometry to quantify OVA-specific $CD8^+$ T cell using SIINFEKL-H-2Kb tetramer staining, and $CD8^+$ T cell effector phenotypes by cytotoxic-associated markers. Our microglia-targeted mOVA LNPs significantly increased OVA-$tetramer^+$ $CD8^+$ T cells in brain and CNS-adjacent immune compartments, including the dura meninges and skull bone marrow. Additionally, brain-infiltrating $CD8^+$ T cells displayed enhanced activation and cytotoxic phenotypes, including increased perforin and granzyme B expression.In summary, we establish microglia-targeted mRNA-LNP delivery as a strategy to

enhance antigen presentation, amplify cytotoxic $CD8^+$ T cell responses, and define a new therapeutic avenue to overcome immune suppression in GBM.

Disclosures: Z. Tian: None. **F. Jin:** None. **M. Maynes:** None. **M. Pedra Seady:** None. **J. Meridew:** None. **A. Tavallaei:** None. **A. Hassani:** None. **A.J. Johnson:** None.

Poster

PSTR267: The Peripheral Immune System in CNS Homeostasis and Disease

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR267.20/Z4

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

Support: NIH Grant 1RF1AG083029

Title: Alzheimer's disease induces lung cholinergic neurotransmission dysregulation in the App^{NL-G-F} mouse model

Authors: *C. CHENG, L. N. KAISER, C. K. COMBS;
Univ. of North Dakota, Grand Forks, ND

Abstract: Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder that is the most common cause of dementia. It is characterized by complex brain pathological changes, including amyloid beta (Aβ) accumulation, neurofibrillary tangles, neuronal degeneration, and neuroinflammation. It has been reported that dysregulation of the cholinergic and adrenergic systems in the brain is linked to the pathophysiology of AD. However, alterations in autonomic function in peripheral organs in AD are less well defined. Increasing evidence shows that in addition to the loss of cognitive function, AD patients also experience respiratory disturbances, whose function is regulated by cholinergic and adrenergic systems. Our previous studies demonstrated increased Aβ levels and an inflammatory response in the lungs of the App^{NL-G-F} mouse model of AD. To better understand respiratory system changes in these mice, we evaluated alterations in the cholinergic and adrenergic neurotransmitter systems in the lungs of male and female 12-month-old C57BL/6 littermate control wild-type and App^{NL-G-F} mice. Western blot analyses and immunohistochemistry were performed to quantify protein levels of choline acetyltransferase (ChAT), tyrosine hydroxylase (TH), and muscarinic acetylcholine receptors, M1-M3, along with ELISAs for estimation of acetylcholine and norepinephrine levels. Widespread ChAT and TH neuronal fiber immunoreactivities were observed in the lungs of both sexes of WT and App^{NL-G-F} mice. Protein levels of TH were not significantly different between WT and App^{NL-G-F} mice. However, female, but not male, App^{NL-G-F} mice had significantly lower ChAT levels compared to their WT controls. ELISA results demonstrated no difference in norepinephrine levels between WT and App^{NL-G-F} mice, but increased acetylcholine levels in the lungs of male App^{NL-G-F} mice compared to WT controls. Correlating with the elevated acetylcholine levels, we observed significantly increased M2 receptor levels only in the lungs of male App^{NL-G-F} mice compared with WT controls, with no differences in M1 or M3 levels in

either male or female mice. Our findings demonstrate that *App*$^{NL-G-F}$ mice exhibit sex-selective dysregulation of the cholinergic system in the lungs. The results suggest a possible disease-related, unique lung-brain axis alteration in AD progression, focusing on the cholinergic system.

Disclosures: C. Cheng: None. **L.N. Kaiser:** None. **C.K. Combs:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.01/Z5

Topic: D.04. Brain Injury and Trauma

Support: 5R01NS122724-04

Title: The Bioflavonoid, Fisetin Exerts Senolytic Activity and Enhances Functional Behavior after Traumatic Brain Injury

Authors: *H. D. SINGH[1], J. WANG[2], Y. LU[1], C. CARR[1], K. M. DHANDAPANI[1], D. W. BRANN[1];
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Abstract: Traumatic brain injury (TBI) is one of the major causes of death and disability in the United States. Recent evidence by our laboratory and others suggests that cellular senescence, where damaged brain cells enter a state of permanent cell-cycle arrest and become proinflammatory, contributes significantly to neuroinflammation and neurodegeneration after TBI. This raises the possibility that therapeutic targeting of senescent cells may have efficacy as a potential treatment for TBI. Therefore, in the current study, we examined whether a short-term intermittent treatment with fisetin, a bioflavonoid with purported senolytic activity, displays senolytic ability and functional benefit after TBI. To determine the senolytic and beneficial actions of fisetin, adult male mice underwent controlled cortical impact (CCI), which produces a moderate TBI. Sham mice without cortical impact and vehicle-treated mice that received cortical impact were included as experimental controls in the study. One week after TBI, intermittent weekly vehicle or fisetin treatment were administered orally for two weeks. The novel object recognition and forced swim behavioral tests were used to evaluate hippocampal-dependent recognition memory and depressive-like behavior, respectively. In addition, Western blot analysis was used to evaluate expression of the senescent marker ($p16^{INK4A}$), and the proinflammatory markers (pStat3 and IL-1β) in the perilesional cortical tissue. The results of the behavioral tests revealed that intermittent weekly fisetin treatment significantly enhanced hippocampal-dependent recognition memory and rescued depressive-like behavior following TBI. Furthermore, intermittent fisetin treatment significantly reduced expression of the senescent marker, $p16^{INK4A}$, and the proinflammatory markers pStat3 and IL-1β, in the perilesional cortex of TBI mice. To our knowledge, our study is the first to demonstrate the senolytic ability of

fisetin after TBI, which may underlie, in part, its beneficial anti-inflammatory and functional benefit after TBI.

Disclosures: H.D. Singh: None. **J. Wang:** None. **Y. Lu:** None. **C. Carr:** None. **K.M. Dhandapani:** None. **D.W. Brann:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.02/Z6

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01NS138370

Title: Pharmacological Activation of AMPK Improves Functional Recovery and reduces Neuroinflammation after TB

Authors: *M. AHMED;
Neurol., Henry Ford Hlth., DETROIT, MI

Abstract: Pharmacological Activation of AMPK Improves Functional Recovery and reduces Neuroinflammation after TB*M. E. AHMED[1], M.S. HUSSAIN[1], A. ABID[1], A.S. AHMAD[1], S. GIRI[1].[1]Department of Neurology, Henry Ford Health, Detroit, MI-48202,Traumatic brain injury (TBI) is a major public health concern and a leading cause of mortality and long-term neurological disability worldwide. AMP-activated protein kinase (AMPK) acts as a critical cellular energy sensor plays a significant role in maintaining cellular energy homeostasis. Emerging evidence suggests that reduced AMPKα1 phosphorylation after TBI disrupts cellular metabolic balance and promotes neuroinflammation; however, the mechanisms by which loss of AMPKα1 activity contributes to neurological dysfunction remain poorly understood. Adult male C57BL/6 wild-type (WT) and AMPKα1 knockout (KO) mice were subjected to TBI or sham surgery. Behavioral tests were evaluated 72h post injury, followed by mice were euthanized and brain tissue were collected for histological and biochemical analyses. We also tested whether pharmacological activation of AMPK could serve as a therapeutic strategy to reduce neuroinflammation and tissue damage after TBI. TBI significantly reduced AMPKα1 phosphorylation in WT mice, while AMPKα1 deficiency in KO mice aggravated behavioral impairments and enhanced activation of the NLRP3 inflammasome, resulting in increased expression of pro-inflammatory mediators including caspase-1 and interleukin-1β. Notably, restoration of AMPKα1 phosphorylation through post -TBI administration of small-molecule activator A-769662 significantly improved neurobehavioral outcomes. These beneficial effects were associated with by reduced blood–brain barrier disruption, decreased neutrophil infiltration, and attenuated inflammasome activation compared with untreated TBI mice. Collectively, these findings suggest that pharmacological modulation of AMPKα1 signalling may represent a promising therapeutic approach to limit

neuroinflammation, reduce secondary brain injury, and improve neurobehavioral outcomes after TBI.

Disclosures: M. Ahmed: None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.03/Z7

Topic: D.04. Brain Injury and Trauma

Support: Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Title: Delivery of neurotrophic factor-α1/ carboxypeptidase E gene in the cortex prevents neurodegeneration, neuroinflammation, and cognitive impairment after mild traumatic brain injury in mice

Authors: A. KHANAM[1], X. YANG[2], D. ABEBE[3], ***Y. LOH**[4];
[1]Section on cellular neurobiology, NICHD/NIH, Bethesda, MD; [2]NIH/NICHD, bethesda, MD; [3]NICHD, NIH, bethesda, MD; [4]NICHD, NIH, Bethesda, MD

Abstract: Background: Concussion is a form of mild traumatic brain injury (mTBI), which causes death and disability among people of all ages and costs ~ $US400 billion annually. MTBI can trigger activation of microglia, which causes neuroinflammation and renders neurons more vulnerable to neurodegeneration. Neurotrophic factor-α1/Carboxypeptidase E (CPE) gene delivery using adeno-associated virus (AAV) has been reported to exert a neuroprotective function in the brains of Alzheimer's Disease mice, reversing neurodegeneration and neuroinflammation. Here, we investigated whether pre-delivery of AAV-CPE into the cortex prior to mTBI can ameliorate neuroinflammation, neurodegeneration, and protect from cognitive impairment. **Methods:** Wild-type (WT) and Atf3-Cre::Snap25-eGFP mice received bilateral stereotaxic injection of either AAV-CPE or AAV-mCherry in +/-1.3 mm lateral from the midline of bregma at 1.5 mm depth, and 14 days later received mTBI in -2 mm lateral from the midline of bregma. In WT mice, amino-cupric-silver staining for degenerating neurons, and immunostaining for CPE, MAP2 (neurites), GFAP (astrocyte), and Iba1(activated microglia) were analyzed in layers 2/3 (L2/3) and layer 5 (L5) of the contralateral cortex and ipsilateral cortex (ipc), 4 days after mTBI. In Atf3-Cre::Snap25-eGFP mice, Atf3+ cells were counted 21 days after mTBI. Novel object recognition (NOR) test was conducted to assess memory impairment 21 days after mTBI. **Results:** An increase in CPE expression was reflected by > 50% higher signal density in Layer 5 of the cortices in AAV-CPE-injected WT mice versus AAV-mCherry-injected mice. In AAV-mCherry-injected mice, after mTBI, both layers of the ipc showed increased numbers of degenerating neurons and reduced MAP2 (neurites). However, AAV-CPE-injection reduced the number of degenerating neurons significantly in both layers and

restored MAP2 (neurites) in layer-5 of ipc. Also, mTBI in AAV-mCherry-injected mice exhibited an increased expression of GFAP and Iba1 in L2/3 of ipc, which was reduced with AAV-CPE-injection. In Atf3-Cre::Snap25-eGFP mice, after mTBI, the number of Atf3+ cells in L5 ipc of AAV-CPE-injected mice was significantly less than that of AAV-mCherry-injected mice . In NOR test, delivery of AAV-CPE improved the impaired memory compared to AAV-mCherry, after the mTBI. **Conclusion:** Our results show that AAV-CPE delivery reduced the number of stressed and degenerating neurons and activated microglia and protected against memory impairment in mTBI-affected mice. Thus, AAV-CPE gene therapy could be a highly effective treatment for concussion.
Key words: TBI; CPE; ATF3; Neuroinflammation; Neurodegeneration.

Disclosures: A. Khanam: None. **X. yang:** None. **D. Abebe:** None. **Y. Loh:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.04/Z8

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant 1R01NS140172-01A1

Title: Dose-response assessment of 2-deoxyglucose dendrimer-pioglitazone in the acute phase after pediatric traumatic brain injury

Authors: *R. MCNEFF[1], A. ARNAOUT[1], A. ABDUL-SATER[1], Y. MASHAL[1], A. DHULL[2], R. SHARMA[2], A. RANI[2], A. SHARMA[2], Z. ZHANG[3];
[1]Univ. of Michigan Dearborn, Dearborn, MI; [2]Washington State Univ., Pullman, WA; [3]Dept. of Natural Sci., Univ. of Michigan-Dearborn, Dearborn, MI

Abstract: Pediatric traumatic brain injury (TBI) triggers neuroinflammation and neuronal injury, yet effective pharmacologic interventions remain limited. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, has demonstrated anti-inflammatory and neuroprotective effects in brain injury; however, its clinical utility is hindered by nonspecific biodistribution, limited brain penetration, and dose-limiting side effects. To overcome these limitations, we created a 2-deoxyglucose-dendrimer conjugate of pioglitazone (2DG-D-pioglitazone) to exploit injury-associated metabolic activity and enhance drug delivery to neurons in the injured brain. The objective of this study was to evaluate the biodistribution, neuronal targeting, and acute dose-response efficacy of 2DG-D-pioglitazone following pediatric TBI. Male and female mouse littermates were randomized at postnatal day 20-21 to Sham, TBI + saline, TBI + free pioglitazone, or TBI + 2DG-D-pioglitazone treatment groups (n = 10 per group, 5 males/5 females). Free pioglitazone or 2DG-D-pioglitazone were administered as a single intraperitoneal dose at 4 hours post-injury at pioglitazone-equivalent doses of 1, 5, or 25 mg/kg. A separate cohort of TBI animals received Cy5-labeled 2DG-D-pioglitazone to assess

biodistribution and cellular localization (n = 4, 2 males/2 females). Sham animals received anesthesia without injury. Behavioral assessments were conducted 24 hours after treatment, and experimental personnel were blinded to treatment assignments. Cy5 imaging demonstrated that 2DG-D-pioglitazone crossed the blood-brain barrier after TBI and preferentially localized to the injured brain region, where the signal colocalized with neurons. Compared with saline and free pioglitazone treatment, 2DG-D-pioglitazone reduced acute neuroinflammatory markers and modulated PPARγ-associated signaling pathways consistent with target engagement. Treatment with 2DG-D-pioglitazone also improved acute functional outcomes, including grip strength and rotarod performance, with effects observed across the tested dose range and greater benefit than equivalent doses of unconjugated pioglitazone. Together, these findings show that 2DG-D-pioglitazone improves targeted pioglitazone delivery to injured neurons after pediatric TBI, enhancing brain localization, reducing acute inflammatory signaling, and improving early motor outcomes compared with free drug. These results define key dosing parameters for acute treatment and support dendrimer-based nanotherapeutics as a promising strategy to improve brain drug delivery while limiting systemic exposure.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.05/Z9

Topic: D.04. Brain Injury and Trauma

Support: Funding source: Veterans Affairs Merit Review Award I01BX004686.

Title: TREM2 deficiency and pharmacologic TREM2 activation in experimental Traumatic Brain Injury (TBI)

Authors: *J. LI[1], A. MIZUMA[1,3], M. KAWABORI[1,4], J. KIM[1,5], R. KACIMI[6], Z. ZHENG[1], L. WANG[7,6], C. L. HSIEH[2], J. SHI[1], **M. A. YENARI**[1];
[1]Neurol., [2]Immunol., Dept of Veterans Affairs Med. Center, Univ. of California, San Francisco, San Francisco, CA; [3]Neurol., Tokai Univ. Sch. of Med., Kanagawa, Japan; [4]Neurosurg., Hokkaido Univ. Hosp., Hokkaido, Japan; [5]Anat., Col. of Med. of Yonsei University, Seoul, Republic of Korea, Seoul, Korea, Republic of; [6]Neurol., Dept of Veterans Affairs Med. Center,

Univ. of California, San Francisco, San Francisco, CA, United States, San Francisco, CA; [7]Neurol., Dept of Veterans Affairs Med. Center, Univ. of California, San Francisco, San Francisco, CA, United States, Palo Alto, CA

Abstract: TREM2 deficiency and pharmacologic TREM2 activation in experimental Traumatic Brain Injury (TBI) Jiakun Li1, Atsushi Mizuma 1,2, Masahito Kawabori 1,3, Jong Youl Kim 1,4, Zhen Zheng 1, Christine Hsieh 5, Jian Shi 1 , Midori Yenari 1 1Dept Neurology, Dept of Veterans Affairs Medical Center, University of California, San Francisco, CA, USA; 2Dept Neurology, Tokai University School of Medicine, Kanagawa, Japan; 3Dept Neurosurgery, Hokkaido University Hospital, Hokkaido, Japan; 4Dept Anatomy, College of Medicine of Yonsei University, Seoul, Republic of Korea; 5Dept Immunology, Dept of Veterans Affairs Medical Center, University of California, San Francisco, CA, USA **Abstract** Traumatic brain injury (TBI) affects millions annually, with no effective treatment. Triggering receptor expressed on myeloid cells 2 (TREM2), expressed particularly on brain microglia and macrophages, regulates their activation and is a potential therapeutic target. To assess TREM2's protective role, male and female TREM2 knockout (KO) and wild-type (WT) mice (n=7/group) were subjected to TBI. TREM2 KO mice of both sexes showed significantly larger tissue damage and more severe neurological deficits compared to sex-matched WT controls. TREM2 KO mice exhibited a pro-inflammatory shift in microglia, indicated by an increase in $iNOS^+/CD68^+$ double-positive cells compared to WT mice, while markedly suppressing phagocytosis. To determine if pharmacologically activating TREM2 might be beneficial, we studied four groups of mice: TBI + TREM2 agonist antibody (TREM2ab), TBI + control antibody (CONab) (n = 8 per group), Sham + TREM2ab, and Sham + CONab (n = 6 per group). The antibody was administered (80 mg/kg IP) immediately and 7 days post-TBI. Sensorimotor function, including body swing and Bederson score, did not differ between treatment groups, but cognitive testing 14 days post-TBI showed a trend toward improved Y-maze performance and a significant increase in unsupported exploration rearing in the open field test in TREM2ab-treated TBI mice compared to CONab controls ($p<0.05$), suggesting enhanced recognition and spatial memory. These findings demonstrate that TREM2 deficiency worsens outcome from TBI by increasing pro-inflammatory responses and inhibiting phagocytosis, while pharmacological TREM2 activation improves cognition. Funding source: Veterans Affairs Merit Review Award I01BX004686.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.06/Z10

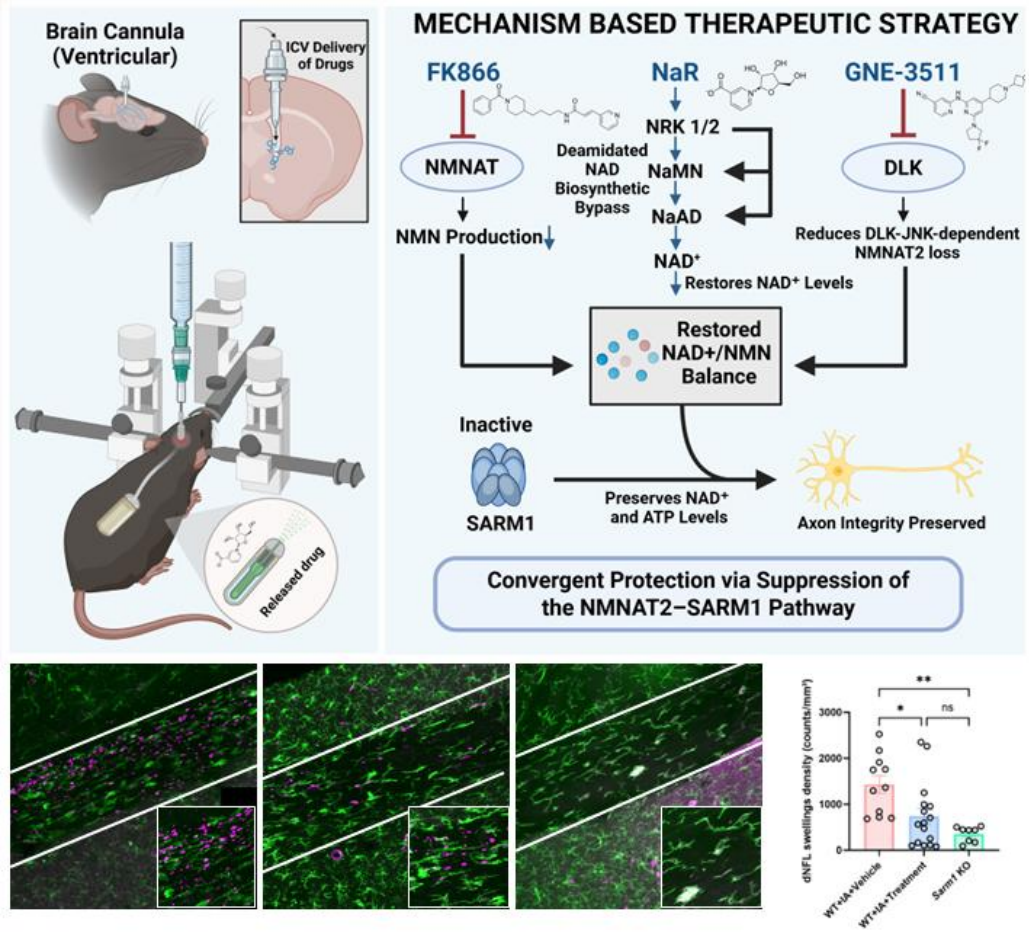
Topic: D.04. Brain Injury and Trauma

Support: NINDS 90092092

Title: Mitigation of traumatic axonal degeneration and demyelination in the visual pathway via targeted pharmacological intervention

Authors: *S. HE, T. AHMED, T. FAZE, A. PENG, A. ALEXANDRIS, V. E. KOLIATSOS; Pathology, Johns Hopkins Univ., Baltimore, MD

Abstract: Traumatic brain injury (TBI) causes progressive white matter injury, where axonal fragmentation and demyelination compromise long-tract connectivity. Within vulnerable tracts, injured axons enter a molecular decision phase driven by dual leucine zipper kinase (DLK) signaling and SARM1-mediated energetic catastrophe. Simultaneously blocking these parallel degenerative pathways represents a rational approach, yet its pharmacological tractability in vivo remains to be fully elucidated. Here, we evaluated a targeted combination pharmacological intervention aimed at concurrently inhibiting both DLK and SARM1 cascades following impact acceleration TBI. In optic tract, axonal pathology was quantified via degraded neurofilament light chain (dNFL) swellings, and myelin architecture via Myelin Basic Protein (MBP). Local neuroinflammation was evaluated by measuring IBA1-positive area coverage across three groups: vehicle controls, pharmacologically intervened animals, and *SARM1* KO controls. TBI induced massive dNFL swelling accumulation and profound demyelination. The targeted pharmacological intervention significantly attenuated dNFL swelling density (P=0.0257) and effectively preserved MBP integrity, phenocopying the structural protection observed in *SARM1*KO benchmarks. Intriguingly, both microglial coverage remained unaltered between vehicle and treated groups. This indicates the therapy exerts robust neuroprotection on the axo-myelin unit without altering gross microglial responses. In conclusion, targeted pharmacological intervention limits traumatic axonal degeneration and demyelination in the visual pathway, highlighting a potential approach for managing progressive neural tract pathology.



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Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.07/Z11

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant 5R01NS121316-03
NIH Grant 1T32GM142520-01A1

Title: Rescue of cognitive deficits and synaptic plasticity using transcranial alternating current stimulation in a mouse model of TBI

Authors: *L. FRAYSER[1], D. GONDALIA[1], J. O'LEARY[1], M. P. BURNS[2];
[2]Dept of Neurosci., [1]Georgetown Univ., Washington, DC

Abstract: Emerging non-invasive brain stimulation techniques, such as transcranial alternating current stimulation (tACS), in which current is passed through the skull in order to modulate neuronal activity through entrainment of oscillatory patterns without altering baseline excitability, represent a possible therapeutic intervention for cognitive deficits following traumatic brain injury (TBI). This study aimed to characterize the behavioral and molecular effects of using tACS at gamma and theta frequencies for treatment in the controlled cortical impact (CCI) model of TBI in mice. Male C57BL/6J mice (n = 27, 8 wks) were subjected to CCI surgery and allowed to recover for 1 month, after which animals were implanted with electrode receptacles for stimulation. All animals were then subject to a pre-treatment T-maze to get a baseline of working spatial memory ability. Mice were randomly assigned to receive either no treatment, gamma frequency tACS (40Hz), or theta frequency tACS (6 Hz). Animal tES stimulators were used to deliver stimulation (0.5 mA) for 20 minutes once per day for three days. A post-treatment T-maze was performed, after which animals were perfused for RT-qPCR analysis of regional gene expression. We found that gamma, but not theta, tACS, was able to significantly increase spontaneous alternation in T-maze, suggesting increased spatial working memory capacity. We found that gamma and theta tACS treated animals had significantly increased expression of synaptic plasticity related genes including BDNF, CAMK2B, and Synaptophysin. Subsequent testing with gamma tACS alone at a lower stimulation intensity (0.2 mA) yielded significant rescue of behavioral deficits in the morris water maze, novel object recognition task, and fear conditioning, but in the absence of significant differences in transcript levels detected by RT-qPCR. From our results we conclude that tACS can rescue cognitive and molecular deficits following TBI in a waveform- and amplitude-dependent manner.

Disclosures: L. Frayser: None. **D. Gondalia:** None. **J. O'Leary:** None. **M.P. Burns:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.08/Z12

Topic: D.04. Brain Injury and Trauma

Support: NINDS # R21 NS114723-01A1

Title: Combination Therapy by Minocycline and Rolipram Delivered by PgP Nanocarrier Improves Motor Function and Mitigates Secondary Injury in a Rat CCI TBI Model

Authors: *H. SHIN[1], B. ELLIOTT[2], A. VANDENBERG[1], N. ABHISARA APPAJI[1], E. AYALA[4], P. O'CONNOR[3], K. WEBB[3], T. A. MURRAY[5], J. LEE[2];
[2]Bioengineering, [1]Clemson Univ., Greenville, SC; [3]Clemson Univ., Clemson, SC; [4]Sch. of Med., Univ. of South Carolina, Greenville, SC; [5]Biomed. Engin., Louisiana Tech. Univ., Ruston, LA

Abstract: TBI is one of the leading causes of injury-related morbidity and mortality. Therapeutic strategies that mitigate secondary injury may improve long-term outcomes. Rolipram (Rm) is a phosphodiesterase 4 (PDE4) inhibitor that can mitigate neu roinflammation by restoring cAMP level, but its application has been hindered by limited solubility, rapid metabolism and systemic side effects. In our lab, we developed a polymeric nanocarrier, poly (lactide-co-glycolide)-graft-polyethylenimine (PgP, US patent 10,232,050 B1) for local delivery of rolipram. Minocycline (Mino) is a tetracycline antibiotic that has shown neuroprotective effects for treatment of TBI. The objective of this study was to evaluate the synergistic effect of Rm-PgP with Mino on neuroinflammation and motor function in a rat moderate CCI TBI model. SD rats (female, 7-8 week) were deeply anesthetized and received craniotomy (6 mm) over the right hemisphere and then impacted using impactor (PSI, velocity: 4 m/sec, depth :2.5 mm, dwell time :250 msec) armed with a 5 mm tip. After surgery, rats were randomly divided into 3 groups: 1) untreated TBI (saline), 2) minocycline alone (saline + Mino), and 3) Rm-PgP with minocycline (Rm-PgP + Mino). Both Rm-PgP (20 µg Rm/rat) and saline were delivered through intraparenchymal injection immediately after injury, and minocycline (50 mg/kg) was administered by i.p. injection daily for 5 days. Motor function was evaluated using rotarod, beam walk, and gait analysis. Rats were sacrificed on the 8th day via cardiac perfusion and brains collected for histological analysis. We observed that Rm-PgP + Mino group showed slightly longer latency compared to untreated and Mino alone group in rotarod test. For beam walk, Rm-PgP + Mino group showed the shortest latency compared to that in untreated and Mino only group. For foot slip test, Rm-PgP + Mino group showed higher recovery (66.6 %), while Mino only group showed lower recovery (37.5%), and untreated group showed lowest recovery (14.3 %) at 7 DPI. For gait analysis, we observed that Rm-PgP + Mino group showed the lowest difference from the baseline for swing, stance, and stride, which indicate best recovery to normal gait. Histologically, we observed reduced lesion volume, neuroinflammation, astrogliosis, and apoptosis and improved neuronal survival in Rm-PgP + Mino group compared to Mino alone and untreated TBI group. These data demonstrate that combination therapy by local Rm-PgP and systemic minocycline synergistically mitigates secondary injury cascades and accelerates functional recovery, offering a highly promising combinatorial platform for clinical TBI management.

Disclosures: H. Shin: None. **B. Elliott:** None. **A. Vandenberg:** None. **N. Abhisara Appaji:** None. **E. Ayala:** None. **P. O'Connor:** None. **K. Webb:** Other; Drs. Lee and Webb are co-Founders and hold equity in NeuroHope Therapeutics, Inc., a small business seeking to develop PgP-based nanotherapeutics for neurotrauma.. **T.A. Murray:** None. **J. Lee:** Other; Drs. Lee and Webb are co-Founders and hold quity in NeuroHope Therapeutics, Inc., a small business seeking to develop PgP-based nanotherapeutics for neurotrauma..

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.09/Z13

Topic: D.04. Brain Injury and Trauma

Support: NIH/NINDS R01NS118166

Title: Hematopoietic growth factors enhance remyelination in white matter during the chronic phase of severe traumatic brain injury

Authors: ***S. LI**[1], R. VALERIO[2], L.-R. ZHAO[2];
[1]Neurosci., [2]Neuroscience/Neurosurgery, SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Severe traumatic brain injury (TBI) leads to long-term white matter degeneration characterized by progressive oligodendrocyte loss and demyelination. However, effective regenerative therapies to enhance remyelination in the chronic phase of severe TBI are lacking. Oligodendrocyte progenitor cells (OPCs), the primary source of new myelinating oligodendrocytes, represent a key therapeutic target for white matter repair. This study aimed to determine whether combined treatment with two hematopoietic growth factors, stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF), in the chronic phase of severe TBI enhances OPC-mediated remyelination. Young adult male and female C57BL/6 mice were subjected to controlled cortical impact-induced severe TBI. At 6 months post-injury, mice received subcutaneous injections of SCF+G-CSF or vehicle solution for 7 consecutive days (n = 5-7 per group). Sham-operated mice served as controls. OPC proliferation was assessed by immunofluorescence for $Olig2^+/Ki67^+$ cells in the corpus callosum (CC) and external capsule (EC) of both hemispheres. To assess newly generated oligodendrocytes, NG2-Cre:ROSA $^{mT/mG}$ mice were used. In this Cre-LoxP model, all cells initially express membrane-targeted Tomato (mT); following tamoxifen-induced Cre activation in $NG2^+$ OPCs, OPCs and their progeny switch to membrane-targeted GFP (mG), enabling identification of newly generated OPC-derived myelin (mG^+/MBP^+) versus pre-existing myelin (mT^+/MBP^+). SCF+G-CSF treatment significantly increased the proportion of proliferating OPCs ($Olig2^+/Ki67^+$) in both ipsilateral and contralateral EC and CC compared to TBI-vehicle controls. TBI-vehicle mice showed minimal mG^+/MBP^+ colocalization, indicating limited OPC-derived myelination during the chronic phase. In contrast, SCF+G-CSF-treated mice exhibited a significant increase in mG^+/MBP^+ cells in ipsilateral white matter regions, demonstrating enhanced generation of OPC-derived myelin. In conclusion, SCF+G-CSF treatment in the chronic phase of severe TBI enhances OPC proliferation and differentiation into myelinating oligodendrocytes, supporting a regenerative mechanism for white matter repair. This study was supported by NIH/NINDS (R01NS118166).

Disclosures: S. Li: None. **R. Valerio:** None. **L. Zhao:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.10/Z14

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01AG082207
NINDS Grant RF1NS135548

Title: Photobiomodulation Attenuates Cognitive Deficits by Reprogramming Hippocampal Microglial Metabolism in Post-Craniectomy TBI

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Abstract: *Background*: Traumatic brain injury (TBI) triggers chronic neuroinflammation and hippocampal-dependent cognitive impairment, often characterized by microglial overactivation. Emerging evidence suggests that microglial activation is energetically sustained by a metabolic shift from oxidative phosphorylation (OXPHOS) to glycolysis. Decompressive craniectomy (DC) is a common lifesaving surgical intervention for severe TBI patients, also creates a potential treatment window for non-invasive interventions. Photobiomodulation (PBM), a non-invasive therapy using near-infrared light, has shown neuroprotective potential, but whether it can alleviate cognitive deficits by directly reprogramming microglial bioenergetics remains to be elucidated. *Methods*: In this study, a controlled cortical impact (CCI) model was established in male C57BL/6 mice. PBM (808 nm, 25 mW/cm², 2 min/day) was administered transcranially over 28 days. Cognitive and motor function were assessed using behavioral tests, bulk RNA-sequencing was performed on both cortical and hippocampal tissues. Primary hippocampal microglia were isolated via CD11b/CD45 magnetic beads to assess real-time mitochondrial respiration (OCR) and glycolysis (ECAR) using Seahorse XF Analysis. In vitro, LPS-stimulated BV-2 cells were treated with PBM to investigate its effects on mitochondrial ROS production, NLRP3 inflammasome activation, and microglial phenotypic switching. *Results*: PBM significantly improved motor coordination and rescued long-term memory deficits. Transcriptomic GSEA revealed that PBM specifically upregulated OXPHOS-related pathways in the hippocampus. Seahorse analysis of isolated microglia demonstrated that PBM restored CCO activity and mitochondrial OCR while inhibiting glycolysis. Mechanistically, PBM-induced metabolic reprogramming suppressed mtROS production, which subsequently inhibited the assembly of the NLRP3 inflammasome. Crucially, pharmacological inhibition of the mitochondrial respiratory chain with Rotenone abolished the neuroprotective effects of PBM, confirming the necessity of the OXPHOS axis. *Conclusion*: These findings collectively demonstrate that 808 nm wavelength PBM treatment effectively promotes functional recovery and cognitive impairments in TBI mice with DC, by driving metabolic reprogramming of hippocampal microglia. It also confirms the security and potential of PBM-based therapeutic strategies in TBI management.

Disclosures: Y. Liang: None. **Z. Huang:** None. **Q. Zhang:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.11/Z15

Topic: D.04. Brain Injury and Trauma

Support: DoD Grant HT9425-24-1-0250

Title: microRNA Therapy Targeting Fibrotic Scar Formation for Improvement of Functional Outcomes after Traumatic Brain Injury

Authors: C. DANILOV[1], Z. WANG[3], L. BERNAL[1], *D. P. HOLSCHNEIDER[2]; [1]Neurosurg., [2]Psychiatry & the Behavioral Sci., USC, Los Angeles, CA; [3]Psychiatry & Behavioral Sci., Univ. of Southern California, Los Angeles, CA

Abstract: INTRODUCTION: Traumatic brain injury (TBI) triggers lesion scar formation that prevents neuronal re-growth and reconnection with target cells, resulting in loss of function. Inhibiting fibrous scar formation could enhance functional recovery. MicroRNAs (miRs) are small noncoding RNAs that regulate gene expression by binding target mRNAs and initiating translational repression or mRNA degradation. Our prior work in a spinal cord injury mouse model showed that miR133b administration specifically targets fibrotic scarring with improved motor outcomes. MATERIAL & METHODS: Using a mouse model of unilateral controlled cortical impact injury (CCI), we examined: (1) optimal timing of IV miR133b intervention by analyzing endogenous miR133b levels at the injury site from 2h-7 days post-injury via RT-qPCR; (2) effects on brain injury via GFAP immunostaining; (3) efficacy in improving cognitive and motor deficits post-TBI; (4) effective dosage based on expression of miR133b target genes, including the fibrogenic (Col1a1) marker; and (5) intranasal administration and brain distribution. RESULTS: (1) CCI altered endogenous miR levels in injured cortex and hippocampus beginning at 2h, persisting through 7 days post-injury; (2) significant tissue loss occurred at the impact site, with increased GFAP staining in deeper ipsilateral regions and contralaterally to a lesser extent; (3) significant motor improvements (grip strength, beam walking) were observed, though cognitive gains (e.g. novel object recognition) were at the non-significant trend level; (4-5) gene expression and intranasal distribution data collection are ongoing, as are experiments using a closed head injury model. CONCLUSION: This is the first study applying miR therapy targeting fibrotic scar reduction in TBI. Completion will provide a framework for understanding how miR therapy remodels lesion scar while evaluating its behavioral, physiologic, and biomarker potential in brain trauma.

Disclosures: C. Danilov: None. **Z. Wang:** None. **L. Bernal:** None. **D.P. Holschneider:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.12/Z16

Topic: D.04. Brain Injury and Trauma

Support: POC IN LABS-UPSaclay TRANSBRAIN INJURY

Title: BRT_002: A Novel Adjunct to Therapeutic Hypothermia for the Treatment of Neonatal Hypoxic-Ischemic Brain Injury

Authors: *A. TSINTZOU[1], C. DISDIER[2], N. COSTA[3], P. GRESSENS[4], X. CHEN[5], R. POIRIER[6], B. S. STONESTREET[7], A. MABONDZO[8];
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Abstract: Exposure to hypoxic-ischemic encephalopathy (HIE) is the major cause of mortality and long-term neurodevelopmental disabilities in newborns. Therapeutic hypothermia (TH) is the only approved treatment for HIE in newborns, but it must be begun within 6 hours after birth for optimal efficacy, and its beneficial effects are limited as 40% of infants still survive with major neurological impairment or die after treatment with TH. Therefore, additional adjunctive or alternative treatments are critically needed to treat HIE. Pharmacological therapies are not currently available. We have previously shown that treatment with the purine derivative, BRT_002, attenuates hypoxic ischemic (HI) brain injury, reduces neuroinflammation, and improves functional recovery in HI-induced neonatal rats. Although BRT_002 appears to have promising effects on HI related brain damage in rodents, the effects of BRT_002 with exposure to TH remain to be determined. Moderate HI was induced in postnatal day 7 (P7) rats using the Rice-Vannucci model. Animals were randomized to Sham, HI+placebo/normothermia (HI+PL/NT), HI+BRT_002/normothermia (HI+BRT_002/NT), HI+placebo/hypothermia (HI+PL/HT), or HI+BRT_002/hypothermia (HI+BRT_002/HT). BRT_002 (30 mg/kg) or vehicle was administered on P7-P9, and animals underwent normothermia (36-37°C) or hypothermia (32-33°C) for 3 h. Outcomes included lesion volume, early motor and reflex development with daily weight monitoring from P7-P10 analyzed by sex. Neuronal, mitochondrial, and intracellular trafficking markers analysis at the transcriptional level in the ipsilateral hemisphere was used to decipher BRT_002 neuroprotective mechanism. BRT_002 reduced HI-induced lesion volume as monotherapy in both sexes and enhanced TH-associated tissue protection in males. BRT_002 alone or combined with TH improved walking performance in both sexes. Righting reflex was unchanged in females, whereas males receiving TH alone showed delayed responses at P10 compared with BRT_002-treated groups. At the molecular level, HI-induced dysregulation of neuronal markers (NeuN, Agrn, Map2, Syt5, Gabbr1, Slc17a7) which was partially normalized by BRT_002 alone and with TH. BRT_002 also reduced Txn2 upregulation, restored Letm1 expression, and ameliorated Pacs1 downregulation, suggesting improved oxidative stress regulation, mitochondrial function, and intracellular trafficking. These findings demonstrate that BRT_002 treatment confers short-term neuroprotection after neonatal HI and provides sex-dependent additive benefit with TH. BRT_002 could represent a clinically relevant adjunct therapy for neonatal HIE.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR268.13/Z17

Topic: D.04. Brain Injury and Trauma

Support: NIH grant R01NS132772-01A1 (YX, LZ)

Title: N-acetyl-seryl-aspartyl-lysyl-proline effects on functional recovery after traumatic brain injury in male rats: therapeutic window and treatment duration study

Authors: *H. PANG[1], X. WANG[2], M. CHOPP[3,5], Y. ZHANG[4], L. CHEN[4], Z. ZHANG[3], L. ZHANG[3,6], Y. XIONG[4,6];
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Abstract: Background: Traumatic brain injury (TBI) causes significant disability and mortality with no effective treatments for improving functional recovery. Our recent study demonstrated that N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP, 0.8 mg/kg/day), improves functional recovery in rats after TBI. This study determines the therapeutic window and duration of AcSDKP treatment after TBI in rats. **Methods:** Adult male Wistar rats (3 month, 250 to 275 g) were randomly divided into seven groups (n=8/group): 1) Sham, 2) TBI+Vehicle, 3-7) TBI+AcSDKP initiated at 1, 2, 6, 24, or 72h post-TBI for 3 days. TBI was induced by unilateral controlled cortical impact. AcSDKP or Vehicle was delivered via subcutaneous osmotic pump. To determine the treatment duration additional groups of male rats were treated with AcSDKP 1h post-TBI for 3, 7, and 14 days. Functional tests were evaluated weekly for 5 weeks using the foot fault, adhesive removal, and modified neurological severity score (mNSS) tests. The Morris Water Maze (MWM) tests were performed on Days 31-35. On Day 35, brains were collected for lesion measurement and histological analysis. **Results:** Compared to Vehicle, AcSDKP significantly reduced the foot fault on Days 7, 14, and 21 post-TBI for all groups, and on Days 28 and 35 for the 1h and 6h groups. AcSDKP improved the mNSS scores for all groups on Day 35, the 1h and 6h groups on Day 28, the 2h and 6h groups on Day 7. In the MWM tests, the AcSDKP reduced latency to reach the hidden platform for 1h group on Days 33-35, while the 6h group showed reduction on Day 33. Additionally, percentage of time spent in the target quadrant increased for the 1h and 2h groups on Days 35. Regarding treatment duration, AcSDKP significantly reduced foot fault on Days 7, 14, and 21 for all groups, with the 3D group maintaining benefits through Days 28 and 35. Adhesive removal time was reduced in the 3D treatment group (Days 7 and 14). All treatment groups improved the mNSS scores on Days 21, 28, and 35. In the MWM test, the 3D group reduced latency to the platform (Days 33-35) and

increased percentage of time spent in the target quadrant (Days 33 and 35). AcSDKP treatments significantly decreased lesion volume compared to the vehicle group. Histological analysis evaluating the effects of AcSDKP on neuroinflammation and neuroprotection is in progress. **Conclusion:** AcSDKP significantly improves functional recovery after TBI, with benefits in motor, sensory, and cognitive outcomes, and reduced lesion volume. Earlier treatment showed more consistent effects. All treatment durations were effective, without clear added benefit beyond 3 days, suggesting that a short early treatment may be sufficient for recovery.

Disclosures: H. Pang: None. **X. Wang:** None. **M. Chopp:** None. **Y. Zhang:** None. **L. Chen:** None. **Z. Zhang:** None. **L. Zhang:** None. **Y. Xiong:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.14/Z18

Topic: D.04. Brain Injury and Trauma

Support: J. William and Katherine C. Asher Endowed Research Fund
Funding from PSY/NEUR department, DePauw University

Title: Bioinformatic Identification and In Vitro Validation of MicroRNA Candidates Targeting S100B in a Traumatic Brain Injury Model

Authors: *T. P. B. VO[1], A. MELSON[2], N. CHOPRA[1];
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and long-term disability worldwide. S100B, an astrocyte-secreted calcium-binding protein, plays a concentration-dependent dual role, exhibiting neurotrophicity at physiological levels but neurotoxicity at the elevated concentrations observed after TBI, driving secondary neuroinflammation and progressive neuronal death. Additionally, S100B is a key acute blood-based biomarker for the diagnosis of TBI. Identifying S100B modulators would identify a novel TBI drug target and describe the factors affecting S100B expression post-TBI. Reducing S100B attenuates neuronal death and shows neuroprotective effects in cerebral ischemia and Parkinson's disease models, yet whether this extends to TBI remains poorly investigated. MicroRNAs (miRNAs) have shown therapeutic promise in neurological disorders. However, there is no miRNA that has been shown to regulate S100B. This study aimed to identify high-value miRNA candidates that putatively target S100B. We queried three bioinformatic algorithms (TargetScan, DIANA-MicroT CDS, MiRbase and PicTar) with the human S100B sequence; PicTar yielded no matches due to S100B's poorly conserved binding sites, and overlapping high-confidence predictions from TargetScan and DIANA-MicroT CDS were filtered to the 99th context++ percentile and cross-referenced against miRBase. Top candidates were transfected using Lipofectamine RNAiMax

into C6 rat glioma cells, and S100B protein expression was quantified by Western Blot and ELISA. This approach identified several high-confidence candidates, with miR-4705 predicted to bind the S100B 3'UTR via an 8-mer site at position 133-140 and retained even at the most stringent threshold. Reduction of S100B was measured in glial cell culture models when compared to transfection controls. Altogether, our results demonstrate a novel mechanism of regulating S100B, with future studies aimed to elucidate its role as a TBI-related neuroinflammation protein and blood-based biomarker.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.15/Z19

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01NS119472

Title: Structural and Functional Connectivity of Human Brain Organoid Grafts with the Rat Motor System

Authors: *S. SINGH[1], J. LEE[2], J. KIM[1], A. LI[3], A. SINGH[4], C. CHAN[5], B. REES[1], S. KUMAR[6], E. NOEL[1], L. VARGAS[1], M. CASTELLANOS[1], P. HARARY[1], Z. ZHANG[1], E. MIRZAKHALILI[7], J. A. WOLF[8], H. SONG[9], G.-L. MING[10], R. BLUE[1], D. JGAMADZE[11], H.-C. I. CHEN[12];
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Abstract: Traumatic brain injury and stroke are among the leading causes of persistent motor deficits in patients, driven largely by neuronal death and the brain's limited capacity for endogenous repair. Transplantation of human cortical organoids offers a strategy to directly replace this injured tissue. Prior work has shown that organoids can integrate with host sensory circuits, but whether grafts can integrate with motor circuitry and drive motor output remains unknown. Here, we combine polysynaptic tracing with optogenetic stimulation to characterize the structural and functional integration of transplanted human cortical organoids with rat motor pathways. Dorsal forebrain organoids were generated from a C1.2-GFP-Cre human iPSC line. Ten rats underwent organoid transplantation into an aspiration lesion in forelimb M1. Five grafts were injected with H129ΔTK-TT, a Cre-dependent anterograde polysynaptic virus, one week

before sacrifice at two months post-transplantation (mpt). Five grafts were injected with a Cre-dependent CaMKIIa-ChR2 two weeks before optogenetic stimulation at two mpt. ChR2+ grafts were stimulated with blue light (470 nm) while recording neural activity from the graft and host caudate-putamen (CPu) and electromyography (EMG) from multiple muscle groups. One-hundred percent of animals and grafts survived. Across animals, over half of the most heavily labeled regions were motor in nature, spanning the cortico-basal ganglia-thalamocortical motor loop. Tracer was visualized as caudal as the cervical spinal cord lower motor neurons, demonstrating graft connectivity through descending host motor circuitry. Optogenetic stimulation of ChR2+ grafts evoked local field potentials (LFPs) not only in the graft but also in the host CPu, a motor region that polysynaptic tracing also identified as structurally connected with the graft. Additionally, sustained oscillatory LFP activity in both the graft and host CPu corresponded with oscillatory EMG activity in the expected contralateral forelimb, linking graft neural activity with somatotopically appropriate motor output. These findings demonstrate that transplanted cortical organoids can integrate both structurally and functionally with host motor circuitry and through polysynaptic connectivity engage in corresponding muscle activity. Organoid transplantation may thus provide a promising strategy for restoring motor function following cortical injury.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Topic: D.04. Brain Injury and Trauma

Support: VA grant IO1BX005708
VA grant IK6BX004214
NIA R25AG086101
VA I01BX005591
VA IKBX005387

Title: Investigating Therapeutic Effects of hASC-sEVs in Repetitive Mild Traumatic Brain Injury and Alzheimer's Disease Related Pathology

Authors: M. ZABRODA[1], O. OGUNSINA[1], C. HUDSON[3], C. LOGAN[1], N. A. PATEL[3], *P. C. BICKFORD[2,3];
[1]Neurosurgery, Brain and Spine, [2]Univ. of South Florida, Tampa, FL; [3]Res. Service, James A Haley VA Hosp., Tampa, FL

Abstract: Traumatic Brain Injury (TBI) is a significant cause of disability and neurodegeneration and is a known risk factor for the later development of Alzheimer's Disease (AD) and AD-related dementias (ADRD). There are many forms of TBI; mild traumatic brain injury (mTBI) is the most common cause of TBI hospitalization, with repetitive mTBI being of particular concern because of its frequency in sports and military settings. TBI is characterized by a long-term neuroinflammatory cascade, along with increases in total Tau, Tau oligomers, Tau hyperphosphorylation, and amyloid precursor protein (APP), all of which may contribute to the development of AD/ADRD. Our lab has used the controlled cortical impact model of TBI (CCI) and showed that treatment 48 hours post CCI with human adipose-derived stem cell small extracellular vesicles (hASC sEVs) reduces brain injury and improves motor and cognitive function while reducing this neuroinflammatory cascade. We report here that sEVs administered intranasally at 7 days post-CCI (sEV dose: 40 x 10e6 particles hASC; CCI method 3 mm impactor at 20^{o} angle centered at 2mm AP and ML from bregma, velocity 4.0 m/s dwell time 300 ms at depth of 0.95 mm) reduces lesion volume size measured using Cavalieri and improves motor behavior deficits immediately post-treatment. We also report data from a closed-head injury mouse model of mTBI. Male C57BL/6 mice (3-6 months old, N= 4-5 per group) were subjected to five closed head injuries (CHI), spaced 48 hours apart, with sham controls anesthetized for the same period of time as the CHI mice without skull impacts (5mm impactor, 5 m/s sec 200 msec dwell time depth 1.0 mm). Mice were administered either 40 x10e6 particles hASC sEVs or PBS vehicle intranasally 48 hours post-last injury. Mice underwent behavioral testing starting 1 dpi, including rotarod, open field, novel object/novel place object recognition, and radial arm water maze (RAWM). Mice were sacrificed 22 dpi, and immunohistochemistry (IHC) was then performed to assess neuroinflammatory markers GFAP, IBA-1, MHC-II, and AD biomarkers APP, Total Tau, pTau 231, and Tau oligomers, along with white matter injury with black gold staining. Behavioral data on rotarod demonstrated a significant interaction between groups over time (repeated measures two-way ANOVA (F (2.858, 17.15) = 3.603, p=0.037). This demonstrates a similar effect of the hASC sEV to improve motor function in both models of TBI. This work does not represent the views or opinions of the US government or the Veterans Administration.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.17/Z21

Topic: D.04. Brain Injury and Trauma

Title: Music-Based Intervention in Pediatric Motor Rehabilitation: a Case Study

Authors: *M. ORTIZ CORTÉS;
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Abstract: Around the world, brain injury is a relevant public health issue. The alternatives in brain injury rehabilitation require the recognition of the patient as a whole human being. This work examined the use of musical stimulation in motor rehabilitation through the lens of the relationship between Neuropsychology and Music from an interdisciplinary perspective. Based on elements taken from Neurologic Music Therapy techniques, a musical stimulation program was designed with the aim of bringing the subject closer to experiencing sound phenomena through the practice of musical events that would positively impact their motor rehabilitation. The subject was a five-year-old patient with a brain injury, whose simple cranial MRI showed left periventricular encephalomalacia and right leucomalacia. Due to the above, he presented spasticity in the lower limbs and the right arm. An instrumental case study of an observational and longitudinal type was conducted. The program lasted 11 weeks, with one session per week, during which activities such as a) rhythmic auditory stimulation, b) patterned sensory enhancement, c) therapeutic instrumental music performance, d) musical listening, and e) group singing were developed. The program's process and product were evaluated through participant observation, which included field diaries, therapeutic progress reports from physiotherapists, and initial and final interviews with the patient's parents. The analysis of the results of this study allowed to affirm that the subject's engagement with musical experiences had a favorable impact on their motor rehabilitation, mainly in two general aspects: 1) Music as motivation for movement and 2) The musical experience as a facilitator of body awareness. This approach enables us to showcase the positive impact of integrating music stimulation into intervention practices for motor rehabilitation.

Disclosures: M. Ortiz Cortés: None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR268.18/Z22

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01-EY038322

Title: Transcription factor regulation of retinal ganglion cell axon regeneration after optic nerve injury

Authors: *J. BRADY, A. LUKOMSKA, B. A. RHEAUME, E. F. TRAKHTENBERG;
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Abstract: Retinal ganglion cells (RGCs) are prototypical central nervous system (CNS) projection neurons which transmit visual information to the brain. As other types of CNS projection neurons, RGCs fail to spontaneously regenerate axons after injury, resulting in permanent loss of vision due to conditions such as trauma, ischemia, and glaucoma. There are currently no approved clinical therapies which induce optic nerve/tract axon regeneration. The neuronal intrinsic factors which contribute to regeneration failure are still not fully understood, and while certain pre-clinical approaches targeting the proclivity of neurons to regenerate have been explored, these generally lead to sparse regeneration from a limited subset of RGCs. Here, we identified a Klf9-associated developmentally downregulated transcriptional regulator (Exp2-TF) whose overexpression results in axon regeneration following optic nerve crush (ONC) injury. Further, we performed single-cell RNA sequencing (scRNA-seq) of RGCs following ONC and treatment with either knockdown (KD) of Klf9 or overexpression (OE) of Exp2-TF. Using bioinformatics analysis of the generated scRNA-seq datasets, we were able to determine that a broad subset of RGC subtypes responded to these treatments by regenerating long-distance axons following treatment. We found that those subtypes most likely to regenerate axons were generally those which retain embryonic-like features in maturity. We also analyzed the downstream gene networks that are regulated by these treatments following optic nerve injury and found substantial overlap in the downstream gene networks associated with axon regeneration, which included several genes known to be involved in axon regeneration. Our findings provide new insights into the mechanisms of optic nerve axon regeneration, in an RGC subtype-specific manner.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR268.19/Z23

Topic: D.04. Brain Injury and Trauma

Support: SECIHTI Grant R-2021-785-080

Title: Environmental enrichment promotes cognitive recovery and increases Iba1+ cell density despite antibiotic-induced microbiota depletion after a moderate pediatric traumatic brain injury

Authors: *J. ZAMUDIO FLORES[1], J. VARGAS BRAVO[1], A. E. KLINE[2], N. LAJUD[1]; [1]Ctr. de Investigación Biomédica de Michoacán, Inst. Mexicano del Seguro Social, Morelia, Mexico; [2]Phys Med. & Rehab, Psych, Safar Ctr. Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Pediatric traumatic brain injury (TBI) is a leading cause of neurological disability, and effective rehabilitation strategies remain limited. Environmental enrichment (EE) promotes

functional recovery after TBI. We recently demonstrated that both TBI and EE modify gut microbiota composition and these changes predict cognitive performance and microglial morphology. However, whether an intact gut microbiota is required for EE-induced recovery remains unknown. Therefore, we evaluated the effect of antibiotic-induced microbiota depletion (AIMD) on cognitive recovery and microglial density following pediatric TBI in animals exposed to EE. Male rats underwent a controlled cortical impact or sham surgery at postnatal day 25 and were subsequently assigned to EE or standard housing (STD). A broad-spectrum antibiotic cocktail consisting of vancomycin (500 mg/L), neomycin (1 g/L), ampicillin (1 g/L) and metronidazole (1 g/L) was administered in drinking water throughout the recovery period. Spatial learning was assessed using the Morris water maze test, and microglial density was quantified by Iba1 immunohistochemistry in the hippocampus and perilesional cortex. TBI+STD animals exhibited impaired acquisition in the Morris water maze compared with sham controls. In contrast, EE improved cognitive performance after TBI regardless of antibiotic treatment. Additionally, EE increased the density of Iba1+ cells in the CA1 region, hilus, and perilesional cortex compared with STD housed animals. No effect of AIMD was observed on cognitive performance or microglial density. In conclusion, AIMD does not mitigate EE-induced cognitive recovery after pediatric TBI. Additionally, EE produced an increase in Iba1+ cell density suggesting a potential role for microglial remodeling in EE-mediated recovery.

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Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Program #/Poster #: PSTR268.20/Z24

Topic: D.04. Brain Injury and Trauma

Support: NIH R35NS132184
VA I01BX006062

Title: Preventing endothelial glycocalyx shedding promotes functional recovery after traumatic brain injury

Authors: *N. GOWTHAMI[1], R. VEMUGANTI[2];
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Abstract: Traumatic brain injury (TBI) leads to significant cerebrovascular dysfunction and secondary injury that leads to neurological deficits. The endothelial glycocalyx is a critical regulator of vascular integrity, and its degradation following TBI worsens brain injury. We investigated whether razuprotafib (AKB-9778), a small-molecule inhibitor of vascular endothelial protein tyrosine phosphatase, protects endothelial glycocalyx integrity and improves

neurological outcomes after experimental TBI. Cohorts of adult male mice (3 months old) subjected to controlled cortical impact (CCI) injury were treated with vehicle or AKB-9778 (60 mg/kg; subcutaneous; five doses in 12h intervals). Sham-operated mice served as control. Endothelial glycocalyx injury was assessed by transmission electron microscopy and plasma levels of syndecan-1 (SDC1) by ELISA. Transmission electron microscopy showed extensive endothelial glycocalyx damage in the ipsilateral cerebral cortex at 24h after TBI. Plasma SDC1 levels significantly increased in TBI/vehicle cohort compared to sham and were significantly reduced in TBI/AKB-9778 cohort compared to TBI/vehicle cohort. AKB-9778 treatment significantly improved the post-TBI motor function recovery compared with vehicle treatment estimated by rotarod test and beam walk test between day 1 and 30 of injury. AKB-9778 treated cohort also showed improved post-TBI cognitive function compared with vehicle treated cohort at days 24 to 27 after TBI estimated by escape latency and probe test in Morris water maze test. Open field test showed increased total distance travelled (indicating improved mobility), but no change in the time in centre (indicating no change in anxiety-like behaviour) in AKB-9778 treated cohort compared with vehicle cohort on day 23 after TBI. Thus, AKB-9778 treatment ameliorated endothelial glycocalyx injury, reduced lesion volume, and improved motor and cognitive functions following experimental TBI. These results indicate that maintaining the integrity of the endothelial glycocalyx may provide a new therapeutic approach to attenuate secondary injury and enhance recovery after TBI.

Disclosures: N. Gowthami: None. **R. Vemuganti:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.21/AA1

Topic: D.04. Brain Injury and Trauma

Support: Dana Foundation First in Man Neuroscience Award
State of California Brain Injury Research Center
Sponsored Research Agreement UCLA-Astrocyte Pharmaceuticals Inc.

Title: Adenosine A1/A3 receptor agonist AST-004 enhances metabolic resilience and structural repair across astrocyte subpopulations, with therapeutic efficacy, target engagement, and injury-defined biomarker responses in a human in vitro trauma platform

Authors: *I. B. WANNER[1], J. LOPEZ[2], M. GONG[2], C. MCMANN-CHAPMAN[3], J. RICHMOND[2], Y. KIM[5], Y. CHEN[2], Y. ZHANG[4], M. KLEE[2], T. LISTON[6], W. KORINEK[6], J. D. LECHLEITER[7];
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Abstract: Traumatic brain injury (TBI) lacks effective therapies to limit neurodegenerative progression. The adenosine receptor agonist AST-004 improves preclinical TBI and stroke outcomes (Liston 2022, Bozdemir 2021) and is currently in two Phase 2 clinical trials for sports-related concussion and mild complicated TBI. To further investigate AST-004 efficacy, dosing parameters, mechanism of action, and pharmacodynamic biomarkers, we used a human *in vitro* trauma platform with cytoanalytic profiling, target engagement assay and astrocyte injury-defined (AID) biomarkers. Pressure-pulse stretch injury induced whiplash trauma in differentiated astrocytes (Wanner 2012; Halford 2017). The molecular signature of *in vitro* differentiated human astrocytes was determined by Tandem-Mass-Tag quantitative proteomics and validated by rank-rank correlation against fetal and mature human brain astrocyte transcriptomic signatures (Zhang 2015). Random, automated imaging quantified membrane disruption via propidium iodide (PI)-uptake. Across a wide range of doses (0.8-100nM), AST-004 reduced PI-uptake with optimal efficacy at lower doses (cubic spline regression, 7 donors). AST-004 reduced cell wounding more effectively than cell death (Cohen's d:1.9-2.9, $p<0.001$, at 48hrs). Repair was fueled by AST-004 elevating mitochondrial membrane potentials by 0.9 SD using live JC10 aggregate/monomer ratiometry ($p=0.01$, at 7hrs). Astrocyte heterogeneity explained 33% of the variance: protoplasmic astrocytes were more resilient than fibrous and transition zone astrocytes. Gray and white matter morphotypes were AST-004 responsive, while transition astrocytes were not (d: 1.9-2.5; $p<0.05$). AST-004 restored the trauma-perturbed fibrous astrocyte pattern ($d=1.4$, $p=0.04$). Immunoblotting confirmed A1 and A3 receptor expression, and staining showed surface and vesicular localization. Both A1 and A3 receptor inhibitors blocked AST-004 repair suggesting dual AST-004 receptor targets ($d=1.2$, $p<0.05$). In addition, AST-004 reduced release of AID biomarkers aldolase C (ALDOC, $d=2$, $p=0.01$, 4-15 samples/group) and GFAP ($d=1.3$, $p=0.028$). Both biomarkers highly correlated with cell damage frequencies further supporting their utility as drug response biomarkers (ALDOC: $R^2=0.85$; GFAP: $R^2=0.7$; $p<0.001$). AST-004 also reduced trauma-induced GFAP proteolysis relevant to post-traumatic astrocyte proteinopathy (Wanner 2026). Together, these human astrocyte data demonstrate that broad nanomolar AST-004 concentration ranges bolster astrocyte mitochondrial bioenergetics, promote cellular repair following cell wounding, and attenuate AID biomarker release.

Disclosures: I.B. Wanner: None. **J. Lopez:** None. **M. Gong:** None. **C. McMann-Chapman:** None. **J. Richmond:** None. **Y. Kim:** None. **Y. Chen:** None. **Y. Zhang:** None. **M. Klee:** None. **T. Liston:** None. **W. Korinek:** None. **J.D. Lechleiter:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.22/AA2

Topic: D.04. Brain Injury and Trauma

Support: NIH/NINDS 5R01NS126273-04
AHA 25TPA1475809

AHA 23TPA1069224
AHA 24SCEFIA1255866
AHA 24TPA1300751

Title: Targeting LXR Signaling to Alleviate Demyelination and Memory Impairment After Traumatic Brain Injury

Authors: Y. ZHOU[1], T. YUAN[1], Z. ZHANG[1], X. TIAN[3], C. Y.-C. WU[1], *R. H.-C. LEE[2,1]; [1]Pharmaceut. Sci., [2]Univ. of South Florida, Tampa, FL; [3]Toxicology and Cancer Biol., Univ. of Kentucky, Lexington, KY

Abstract: Traumatic brain injury (TBI) is a major cause of death and disability in both military and civilian populations, impacting 1.5 million individuals in the U.S. TBI survivors often experience severe brain damage and loss of memory. Demyelination is a notable pathological consequence of traumatic brain injury (TBI), which has a devastating impact on brain function, memory, and cognition. This is because myelin sheaths' essential role in providing insulative protective coverings for neuronal axons, facilitating the propagation of nerve impulses. Therefore, the major challenge of post-TBI care is to alleviate demyelination. As such, liver X receptor (LXR) is a nuclear receptor that plays a crucial role in lipid metabolism and cholesterol homeostasis. Previous studies indicated that enhanced LXR signaling can promote cholesterol levels in oligodendrocytes, the cells responsible for myelin formation in the central nervous system, to support oligodendrocyte maturation and remyelination. We thus hypothesize that treatment with GW3965, a synthetic agonist of LXR, to activate LXR signaling can alleviate demyelination and memory deficits following TBI. Method: C57BL/6 mice were subjected to closed head injury (CHI) using a stereotaxic precise impactor (RWD Life Science, velocity 5.1 m/s, depth 1.00 mm, and dwell time 80 ms). GW3965 was administrated via oral gavage one day following TBI for two weeks (10 mg/kg/day). Following treatment, memory- and cognition-related behavioral tests (e.g., novel objection recognition test and Y-maze) were conducted. Myelin pathology was further assessed by immunofluorescence staining and capillary-based immunoassay. Results: Our results indicate that treatment with GW3965 significantly reduced TBI-induced demyelination via myelin basic protein, microtubule-associated protein 2, and axonal membrane protein (Caspr). In addition, mice treated with GW3965 had better behavioral test performance following TBI as compared to untreated animals. Our findings suggest that targeting LXR signaling is a potential therapeutic approach in the treatment against TBI-induced myelin pathologies and associated cognitive impairments.

Disclosures: Y. Zhou: None. **T. Yuan:** None. **Z. Zhang:** None. **X. Tian:** None. **C.Y. Wu:** None. **R.H. Lee:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.23/AA3

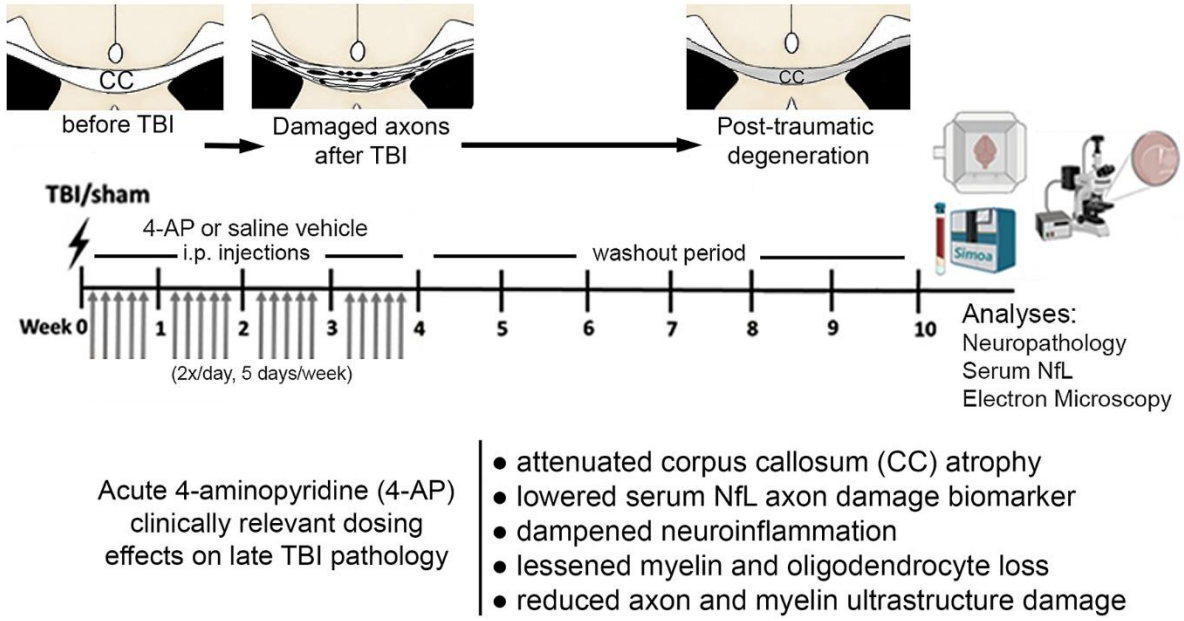
Topic: D.04. Brain Injury and Trauma

Support: Military Traumatic Brain Injury Initiative (MTBI2) Award HU0001-23-2-0071
United States Defense Health Agency Program in Brain Injury and Disease Prevention, Treatment, and Research Award HU0001-25-20039
Congressionally Directed Medical Research Programs Award W81XWH-21-2-0040

Title: Disease-modifying effects on chronic axon damage and white matter degeneration with 4-aminopyridine after acute traumatic brain injury

Authors: *K. RADOMSKI[1,2], X. ZI[1,2,3], G. M. SULLIVAN[1,2,3], R. C. ARMSTRONG[1,2]; [1]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [2]Military Brain Injury Initiative (MTBI2), Bethesda, MD; [3]The Henry M. Jackson Fndn. for the Advancement of Military Medicine, Inc., Bethesda, MD

Abstract: Axonal injury is a hallmark pathology of acute traumatic brain injury (TBI) that drives degeneration of white matter in chronic TBI and in neurodegenerative diseases. No available therapies effectively treat damaged axons. We focused on early, potentially reversible, axonal pathologies of abnormal nodes of Ranvier and demyelination as intervention targets. 4-aminopyridine (4-AP), which blocks potassium Kv channels, is an FDA-approved drug prescribed for multiple sclerosis to enhance axon signal conduction through nodes with Kv channels exposed by demyelination. We hypothesized that early 4-AP treatment after acute TBI could mitigate secondary axon damage and white matter degeneration. Adult male and female mice received a nonpenetrating TBI or sham procedure. A low clinically relevant dose of 4-AP (0.5 mg/kg, b.i.d.) or saline vehicle was initiated at 24 hours, administered over 4 weeks, then discontinued for 6 weeks prior to analysis at 10 weeks post-injury. TBI caused atrophy of corpus callosum (CC) white matter and increased serum neurofilament light (NfL) protein, a translational biomarker of axonal injury. 4-AP treatment after injury significantly attenuated CC atrophy and lowered serum NfL levels. 4-AP also significantly lessened CC myelin and oligodendrocyte loss while dampening neuroinflammation, i.e. astrogliosis and microgliosis. In a parallel electron microscopy study, 4-AP reduced intra-axonal structural damage and mitochondrial swelling, normalized axon diameters, and increased myelin thickness. These findings reveal 4-AP disease-modifying effects on the progression of evolving TBI pathology that endure long after discontinuing treatment. More broadly, these results demonstrate proof-of-concept support for developing interventions to treat axon damage and white matter degeneration.



Disclosures: K. Radomski: None. **X. Zi:** None. **G.M. Sullivan:** None. **R.C. Armstrong:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.24/AA4

Topic: D.04. Brain Injury and Trauma

Support: Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement HR00112420337. All views, opinions, and findings are those of authors and do not represent the official views of the Department of Defense or the U.S. Government.

Title: Effects of acute, pre-injury stress on chronic spatial working memory deficits caused by severe traumatic brain injury in rats

Authors: *A. SANJANA[1], C. HSIEH[1], T. WROBLEWSKI[1], A. MEJIA-BAUTISTA[1], T. RODRIGUEZ[2], P. A. SERRANO[2], D. S. LING[1];
[1]Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [2]Dept of Psychology, Hunter College, CUNY, New York, NY

Abstract: Cognitive dysfunction is a major pathological sequel of traumatic brain injury (TBI). We have shown that prophylactic administration of brivaracetam (BRV) may provide neuroprotection against TBI-induced spatial working memory deficits, modeled via controlled cortical impact (CCI) injury in rats. In this study, we examined the effects of pre-injury acute

stress on post-injury spatial working memory. Rats (aged P25-36) were randomly assigned to receive 1 h of elevated platform stress (EPS) followed by a 5-min open field test (OFT), approximately 1 h before CCI injury. Stress-controls (i.e., no stress) were not subjected to EPS, while sham-injury controls were not subjected to CCI. Rats were randomly assigned to receive either a single IP dose of BRV (21 mg/kg) or the saline vehicle at 15 -20 min prior to CCI. At 5 - 8 weeks post-injury, rats were assessed for spatial memory function using a 4-day active place avoidance (APA) test. Performance was assessed using four metrics: (1) time to first shock-zone entry, (2) total number of shock-zone entries, (3) percentage of time spent in the shock zone, and (4) maximum shock-zone avoidance time. CCI rats that were not subjected to pre-injury EPS (no stress-CCI) exhibited significant deficits in spatial memory performance across all four APA metrics relative to sham-injury controls. However, CCI rats that received a 1 h pre-injury exposure to EPS (stress-CCI) performed significantly better on APA, exhibiting spatial memory function equivalent to sham controls. Furthermore, stress-CCI rats that received a single dose of BRV prior to injury (stress-CCI-BRV) also exhibited APA performance equivalent to sham controls, indicating that acute, pre-injury stress did not interfere with the neuroprotective effects of BRV. On the contrary, with rats that were exposed only to stress (i.e., stress-no CCI), we found that 50% of the rats demonstrated significant deficits in APA performance, whereas, the other 50% performed as well as non-stressed controls. These findings suggest that pre-injury exposure to acute stress may provide neuroprotection against TBI-induced spatial working memory deficits, which does not interfere with the prophylactic neuroprotective actions of BRV.

Disclosures: A. Sanjana: None. **C. Hsieh:** None. **T. Wroblewski:** None. **A. Mejia-Bautista:** None. **T. Rodriguez:** None. **P.A. Serrano:** None. **D.S. Ling:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

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Topic: D.04. Brain Injury and Trauma

Support: Defense Advanced Research Projects Agency (DARPA) under Cooperative Agreement HR00112420337. All views, opinions, and findings are those of authors and do not represent the official views of the Department of Defense or the U.S. Government.

Title: Effects of Acute Pre-Injury Stress and Prophylactic Brivaracetam on Spatial Working Memory and Anxiety-Like Behaviors Following Traumatic Brain Injury

Authors: *T. M. RODRIGUEZ[1], M. MORRIS[2], N. A. FERGUSON[3], M. AGUILAR[4], S. DUMIC[3], N. RAIHANA[4], S. GYRLA[3], P. DAVE[3], E. OZGA STASIEWICZ[3], A. OSKON[4], J. GYRLA[4], A. SANJANA[5], D. S. LING[6], P. A. SERRANO[3];
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New York, NY; [3]Psychology, [4]Biol., Hunter College, CUNY, New York, NY; [6]Physiol. and Pharmacol., [5]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY

Abstract: Traumatic brain injury (TBI) promotes excessive glutamate release, resulting in glutamatergic receptor overactivation, disruption of intracellular calcium (Ca2+) homeostasis, and neuronal dysfunction in the hippocampus and prefrontal cortex. These pathological changes contribute to post-traumatic epilepsy (PTE), which is associated with short-term memory deficits and anxiety-like behaviors. Pre-injury stress may further exacerbate glutamate release, excitotoxicity, and neuroinflammation, worsening these impairments. To date, no effective therapy has been established to prevent PTE, which is often irreversible and resistant to current anti-seizure medications (ASMs). We previously demonstrated that prophylactic administration of Levetiracetam (LEV; 150 mg/kg) prior to TBI improves spatial working memory and attenuates anxiety-like behavior in the controlled cortical impact (CCI) model of TBI in male Sprague Dawley (SD) rats. Similarly, prophylactic Brivaracetam (BRV; 2.1 mg/kg) reduced anxiety-like behavior and increased exploratory activity post-injury. This study investigates the effects of acute stress exposure prior to TBI and whether prophylactic BRV reduces spatial working memory deficits and anxiety-like behaviors. We hypothesize that acute stress exposure prior to TBI will exacerbate these impairments, whereas prophylactic BRV (2.1mg/kg) administration will attenuate them. Male SD rats (P42-57) were randomly assigned to 1 h of pedestal stress or no-stress (home cage) control conditions, followed by a 5-min open field test (OFT). Post-OFT, rats underwent either CCI (6.0-mm diameter impactor; 2.0-mm depth) or no injury. 15-20 minutes prior to injury, rats received a single intraperitoneal injection of BRV (2.1 mg/kg) or vehicle (0.9% saline). The radial 8-arm maze (RAM) assessed spatial working memory, and the elevated plus maze (EPM) evaluated anxiety-like behavior at 1 month post-injury. Preliminary RAM findings demonstrate that BRV pretreatment significantly reduced working memory errors in No TBI + No Stress animals compared to vehicle-treated controls and TBI + Stress + Vehicle animals, suggesting a potential procognitive effect in non-injured, unstressed rats. In EPM, TBI + No Stress + Vehicle rats spent more time in the closed arms than No TBI + No Stress + Vehicle controls, indicative of increased anxiety-like behavior following injury, whereas no significant differences were observed in open-arm time. Additional outcomes are under investigation. Ongoing analyses will evaluate the effects of TBI, acute stress pre-exposure, and BRV on spatial working memory, anxiety-like behavior, and neuroprotection.

Disclosures: T.M. Rodriguez: None. **M. Morris:** None. **N.A. Ferguson:** None. **M. Aguilar:** None. **S. Dumic:** None. **N. Raihana:** None. **S. Gyrla:** None. **P. Dave:** None. **E. Ozga Stasiewicz:** None. **A. Oskon:** None. **J. Gyrla:** None. **A. Sanjana:** None. **D.S. Ling:** None. **P.A. Serrano:** None.

Poster

PSTR268: Brain Injury: Therapeutic Strategies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR268.26/AA6

Topic: D.04. Brain Injury and Trauma

Support: The Defense Advanced Research Projects Agency (DARPA) under the Cooperative Agreement HR00112420337 (to D.S.F.L. and P.A.S)

Title: Prophylactic Levetiracetam Efficacy in Reducing Traumatic Brain Injury-Induced Working Memory Deficits and Anxiety-Like Behaviors

Authors: *E. OZGA STASIEWICZ[1], T. RODRIGUEZ[3,1], O. MUTWALI[1,4], M. MORRIS[1,4], S. GYRLA[1,2], S. DUMIC[1,2], P. DAVE[1], M. AGUILAR[1,4], N. A. FERGUSON[1], N. RAIHANA[1], A. SANJANA[5,6,7], D. S. LING[5,6,7], P. A. SERRANO[1,3,4,2];
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Abstract: Traumatic brain injury (TBI) leads to the development of post-traumatic epilepsy (PTE), resulting in memory deficits and heightened anxiety responses. No effective treatments exist to prevent PTE, as current anti-seizure medications (ASMs) fail due to missed critical therapeutic windows. Early administration of the ASM, levetiracetam (LEV), has been shown to suppress epileptiform activity by targeting synaptic SV2A and increasing calcium influx, therefore modulating excessive glutamate release. We hypothesized that prophylactic administration of LEV (150 mg/kg), 15-20 minutes prior to TBI, would reduce working memory deficits and anxiety-like behaviors one month post-chronic injury. Using a controlled cortical impact (CCI) model in male Sprague-Dawley (SD) rats, animals were randomly assigned to TBI + Vehicle (0.9% saline), TBI + LEV (150 mg/kg), or No TBI + Vehicle groups. LEV (150 mg/kg) was administered 15-20 minutes before injury. One month post-TBI, working memory was assessed using the radial 8-arm maze (RAM), and anxiety-like behaviors were evaluated using the elevated plus maze (EPM). Findings indicate that LEV treatment significantly improved working memory scores in RAM: TBI + LEV rats committed fewer working memory errors compared to TBI + Vehicle. In the EPM, no TBI rats spent significantly less time in closed arms compared to TBI + Vehicle rats, indicating that the TBI induced working memory deficits in injury rats. TBI + Vehicle rats spent more time in closed arms compared to LEV-treated rats, indicating that LEV may have worked effectively at reducing working memory errors post-injury. These findings suggest that early prophylactic administration with LEV may mitigate long-term cognitive deficits following TBI, indicating a possible intervention previous to TBI recovery.

Disclosures: E. Ozga Stasiewicz: None. **T. Rodriguez:** None. **O. Mutwali:** None. **M. Morris:** None. **S. Gyrla:** None. **S. Dumic:** None. **P. Dave:** None. **M. Aguilar:** None. **N.A. Ferguson:** None. **N. Raihana:** None. **A. Sanjana:** None. **D.S. Ling:** None. **P.A. Serrano:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.01/AA7

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: ERA·NET Joint Call 2021 (PRECRISCI)
The Scientific and Technological Research Council of Türkiye (TUBITAK) (1221N519)

Title: PLLA and graphene-functionalized PLLA piezoelectric nerve conduits for spinal cord repair: functional and histological outcomes in a rat injury model

Authors: *G. SENGUL[1], E. CANDAR[2], U. STACHEWICZ[4], P. SZEWCZYK[4], A. SENDEMIR[3];
[1]Ege Univ, Sch. Med., Izmir, Turkey; [2]Neurosci., [3]Ege Univ., Izmir, Turkey; [4]AGH Univ. of Krakow, Krakow, Poland

Abstract: Spinal cord injury (SCI) remains a major cause of permanent neurological disability, and biomaterial-based approaches are increasingly investigated to support tissue repair and functional recovery. This study evaluated poly(L-lactic acid) (PLLA) and graphene-functionalized PLLA (PLLA+rGO) piezoelectric nerve conduits in a rat model of SCI.Fifty-four adult male Sprague-Dawley rats underwent T8-T9 compression injury induced with an aneurysm clip after laminectomy. Animals were assigned to SCI-only, SCI+PLLA, or SCI+PLLA+rGO groups, with tissue collected at 14, 28, and 72 days. Functional recovery was assessed using the Basso, Beattie, and Bresnahan locomotor scale. Immunofluorescence for GFAP, NeuN, NF-200/ANF, MBP, MPO, and CD68 was used to evaluate astroglial activation, neuronal survival, axonal integrity, myelin preservation, inflammation, and microglial/macrophage activation. SCI-only animals showed severe tissue damage, including lesion cavitation, dense GFAP-positive glial scar formation, marked neuronal loss, myelin disruption, persistent CD68 immunoreactivity, and limited axonal preservation. Both conduit-treated groups showed improved locomotor recovery and more favorable tissue organization than untreated SCI animals. However, PLLA alone produced the most favorable outcome. Histopathological findings across the 14-, 28-, and 72-day groups supported this interpretation: SCI+PLLA showed better preservation of myelin structure (MBP), less severe neuronal loss (NeuN), a less pronounced astroglial response (GFAP), and a more favorable pattern of axonal integrity/regeneration (ANF/NF-200). In contrast, SCI+PLLA+rGO showed more marked GFAP staining, indicating a stronger astroglial response, together with higher MPO and CD68 immunoreactivity, consistent with increased inflammation compared with SCI+PLLA. These findings indicate that PLLA-based piezoelectric nerve conduits support recovery after experimental SCI by creating a permissive microenvironment for preservation and repair. Although both PLLA and PLLA+rGO improved outcomes compared with untreated SCI, graphene functionalization did not provide an additional therapeutic advantage under the present conditions. PLLA alone merits further investigation as a scaffold candidate for spinal cord repair.

Disclosures: G. Sengul: None. **E. Candar:** None. **U. Stachewicz:** None. **P. Szewczyk:** None. **A. Sendemir:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.02/AA8

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: P0028319
RS-2024-00419269

Title: Wireless spinal electrical stimulation promotes motor recovery after contusive spinal cord injury in rats and minipigs

Authors: *D. KIM[1], J. HYUN[2];
[1]Ajou Univ., Suwon-si, Korea, Republic of; [2]Physical Med. & Rehabil., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: Spinal cord injury (SCI) disrupts spinal neural circuits and causes persistent motor dysfunction. Electrical stimulation can enhance post-injury neuroplasticity, but conventional rigid spinal electrodes have limited conformity to the injured cord and may cause mechanical mismatch. To address these limitations, we developed an ultra-soft wireless spinal electrical-stimulation interface composed of a carbon-silicone composite neural interface and an implantable wireless stimulator. The compliant full-coverage interface was designed to surround the injured spinal cord and deliver spatially distributed stimulation without focal compression. This study primarily tested whether early wireless spinal stimulation promotes motor recovery after thoracic contusive SCI in rats, with additional large-animal validation in minipigs. Female Sprague-Dawley rats underwent moderate thoracic contusion injury followed by immediate implantation and were assigned to 1-V stimulation or non-stimulation groups. Electrical stimulation was delivered daily for 3 consecutive days, and locomotor recovery was assessed for 8 weeks using the Basso-Beattie-Bresnahan (BBB) locomotor rating scale and horizontal ladder walk test. Compared with non-stimulated controls, 1-V stimulated rats showed significantly greater locomotor recovery, with higher BBB scores and improved ladder performance during the post-injury observation period. Histological analysis demonstrated reduced lesion cavity formation and increased 5-HT-positive axonal fibers in rostral and lesion-center regions, suggesting enhanced serotonergic axonal sprouting, tissue preservation, and remodeling of descending modulatory pathways. These rat data indicate that early 1-V wireless spinal stimulation improves functional recovery and modifies structural pathology after contusive SCI. To examine large-animal feasibility, a scaled-up device was implanted in female minipigs after thoracic contusion, and transcutaneous wireless stimulation was delivered at 6 or 12 V through a subcutaneous receiver connected to a spinal cord-surrounding electrode. In minipigs, stimulation produced observable motor improvement and reduced histological tissue damage, with more consistent recovery under the 6-V condition than the 12-V condition. Together, these findings show that ultra-soft wireless spinal stimulation promotes motor recovery after contusive SCI, primarily demonstrated in the rat 1-V stimulation model and supported by minipig validation.

This approach may provide a mechanically compliant neuromodulation strategy for further translational development in SCI.

Disclosures: D. Kim: None. **J. Hyun:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.03/AA9

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: DNA & RNA Changes in Response to Electrical Stimulation in Spinal Cord Injury

Authors: *J. D. LESNY DRAKE[1,2], J. MEJIA[1,2], M. HOGAN[1], P. J. HORNER[1,2];
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Abstract: We largely investigated the DNA and RNA changes in the spinal cord following electrical stimulation, a common therapeutic to treat spinal cord injury. Specifically, we wanted to understand the role of DNA damage in spinal cord tissue after electrical stimulation. Rats were stimulated both acutely and subacutely to characterize differences in their presentations of affected DNA. Unilateral DNA damage was present near the site of stimulation acutely. We found that DNA damage preferentially occurs in specific cell types, depending on the stimulation and injury paradigm. We also were interested in specific activity-dependent genes following electrical stimulation, which we identified from a bulk RNAseq data set. Thus, we quantified RNA changes in these genes of interest after injury and subsequent electrical stimulation. We identified and analyzed the differences in how these genes manifest. Broadly, this work will help elucidate the cellular and molecular mechanisms of electrical stimulation used to treat spinal cord injury.

Disclosures: J.D. Lesny Drake: None. **J. Mejia:** None. **M. Hogan:** None. **P.J. Horner:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.04/AA10

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH NS104194
Craig H Neilsen Foundation

Title: H-Reflex Relationships To Spastic Collapse And Spasms in Adult Spinalized Rats With AAV-delivered BDNF And Epidural Stimulation

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Abstract: After adult complete spinal cord injury (SCI) in rats at the T10 segmental level treated with viral AAV-BDNF therapy below the lesion, rats hindlimbs can step in alternation reflexively. Rats then make further significant gains in function with robot rehabilitation at the pelvis, using an assist-as-needed control. However, about 40% of rats after the initial functional gains later begin to show spasms interfering with weight-bearing and stepping, progressively causing a major collapse in function within the first 6 weeks of treatment. Adding epidural stimulation with the AAV-BDNF treatment significantly delays any collapse for over 4 weeks, beyond the 6 week window, but not permanently. We collected H-reflex data in such rats chronically, examining the reflex before, during and at the end of rehabilitation. We compared H to M ratio and Rate/ Frequency Dependent Depression (RDD/FDD) at time points throughout. After SCI, rats immediately showed loss of RDD and increase in H vs M before any rehabilitation had begun. In all rats with viral BDNF, the H to M ratio and reflex RDD then recovered to near normal, throughout the rehabilitation in the period during significant functional gains. Some rats maintained a plateau of function, while others showed collapse. We compared H-reflex in rats with spasticity, spasms, and collapse before, during and after the gains in function and subsequent collapse. At peak function rats with subsequent collapse and those without any collapse did not differ in H-reflex RDD, which was near intact levels. As collapse and spasms began the H-reflex RDD declined. By full collapse rats' RDD was the same or worse than rats' RDD immediately post SCI, but the non-collapsing rats' RDD was preserved. During collapse in rats there was first an emergence of flexor spasms, and this was later followed by addition of extensor spasms. H-reflex H:M ratio changes in the rats showing collapse preceded both the RDD and the collapse by about a week. H:M and RDD initial changes may thus predict the subsequent emergence of spasms, and accompany the collapse. These measures might form useful biomarkers to manage BDNF positive and negative treatment effects in post SCI spinal cord. Epidural stimulation modifies the long-term dynamics of this spasm development and collapse processes in the context of AAV-BDNF treatment of the SCI spinal cord. Further, ongoing and future work identifying the sources and the mechanisms of collapse and its amelioration can in future enable customized optimization of individual therapies and functional rehabilitation after SCI.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR269.05/AA11

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Craig H Nielsen Foundation Award #1519647

Title: Epidural stimulation for bowel function in spinally contused rats

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Abstract: Restoration of autonomic functions, including cardiovascular, lower urinary tract, and bowel function, remains a high clinical priority for individuals living with spinal cord injury (SCI). Spinal cord epidural stimulation (scES) has demonstrated the ability to modulate autonomic circuits involved in bowel function following SCI without adversely affecting cardiovascular regulation. Despite its therapeutic promise, the mechanisms underlying scES-mediated improvements remain poorly understood, and systematic approaches for identifying optimal stimulation sites and parameters are needed. In the present study, a clinically relevant rodent T9 moderate-severe contusion (215kdyn) SCI model was used to characterize bowel dysfunction and evaluate scES parameter-dependent responses. Terminal experiments consisted of stimulation parameter mapping conducted at the T13 and L6 spinal segments. Outcome measures included external anal sphincter electromyography (EAS-EMG) and anorectal manometry to assess rectal contractile activity at 0, 2, and 4 cm from the anal verge. Stimulation-dependent differences were observed in both EAS activation and rectal contraction frequency. Specifically, stimulation frequencies in the 30 Hz range elicited greater responses than frequencies in the 10 Hz range across both outcome measures. While stimulation at 60 Hz produced effects comparable to those observed at 30 Hz, it also induced substantial activation of hindlimb and back musculature, suggesting reduced specificity. These findings indicate that 30 Hz stimulation may provide an effective balance between promoting bowel-related responses and minimizing off-target motor activation. Collectively, these results provide insight into the optimization of scES parameters for the treatment of bowel dysfunction following incomplete SCI. Improved understanding of stimulation-dependent effects on continence- and defecation-related circuitry may inform clinical management approaches and provide specific targets for the improvement of neuromodulatory strategies.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

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Title: A Novel TMS Platform for Small Non-Human Primates: Transcriptomic and Anatomical Evidence of Axonal Sprouting and Motor Recovery in Spinal Cord Injury

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Abstract: Introduction: Transcranial magnetic stimulation (TMS) is a non-invasive approach to enhance neural plasticity. However, its therapeutic mechanisms in spinal cord injury (SCI) remain unclear. Rodent models poorly predict human responses due to widespread stimulation artifacts and different neuroanatomy. To bridge this translational gap, we developed the first TMS platform for a small non-human primate, the common marmoset, and examined the therapeutic effects of TMS in acute cervical SCI.Methods: We developed a custom stereotaxic fixation and motor-evoked potential (MEP) recording system for marmosets. The primary motor cortex (M1) was targeted using MRI-guided neuronavigation. In healthy subjects (n=3), we applied intermittent theta-burst stimulation (iTBS) and monitored MEP amplitude changes. Electric fields were evaluated via scalar potential finite difference simulations. We investigated the therapeutic potential of iTBS in a left C4/C5 lateral hemisection SCI model. Animals received right M1-targeted iTBS or sham stimulation daily for 7 weeks starting one day post-injury (n=4/group). Forelimb motor recovery was longitudinally assessed double-blind using an open-field scoring system. At 7 weeks post-injury, intracortical microstimulation (ICMS) was performed to map motor cortical representation. Anterograde tracing used biotinylated dextran amine (BDA) injection into the stimulated M1. Single-nucleus RNA sequencing (snRNA-seq) of M1 was conducted at 2 weeks post-injury.Results: In healthy marmosets, iTBS significantly increased normalized MEP amplitudes post-stimulation ($p<0.01$), mirroring human responses and indicating enhanced corticomotor excitability. MRI-based simulations confirmed the electric field was focused in the target hemisphere at the motor threshold. In the SCI model, the iTBS group showed significant upper extremity motor recovery from week 4 ($p<0.05$). ICMS revealed preservation of wrist-related motor representation in the iTBS group. BDA tracing showed increased descending axonal sprouting below the lesion ($p<0.05$). BDA-labeled corticospinal

tract (CST) axons co-localized with the presynaptic marker synaptophysin. snRNA-seq analysis identified a cluster of subcerebral projection neurons including the CST, revealing that iTBS upregulated genes linked to axon guidance and synaptic adhesion.Conclusions: We developed a novel non-human primate TMS platform that mimics human-like neuromodulatory responses. Our findings provide strong evidence that iTBS significantly enhances motor recovery and promotes structural neural reorganization after acute cervical SCI.

Disclosures: T. Shimizu: None. **N. Nagoshi:** None. **T. Kondo:** None. **Y. Sato:** None. **J. Hata:** None. **K. Muta:** None. **H. Tamada:** None. **M. Sekino:** None. **J. Tabata:** None. **H. Okano:** None. **M. Nakamura:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

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Title: rTMS promotes rapid corticospinal tract plasticity and recovery of dexterous hand function after cervical spinal cord injury in macaques

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Abstract: Spinal cord injury (SCI) at the cervical level can lead to hand paralysis. Our laboratory has demonstrated that although spontaneous recovery after mid-cervical subhemisection is slow and limited in nonhuman primates, combining rehabilitative training with electrical stimulation of the motor cortex via subdural electrodes enhances motor functional recovery (Yamaguchi et al., 2023). For clinical translation, we sought to develop a noninvasive stimulation approach using repetitive transcranial magnetic stimulation (rTMS) to achieve comparable recovery in the same SCI model. We trained six monkeys (Ah, Sa, Da, Mo, Mi, and Ko) to perform a reach-and-grasp task designed to assess finger dexterity, followed by a cervical subhemisection at the C4-C5 border. In monkeys Da, Mo, Mi, and Ko, we implemented rehabilitation combined with a novel rTMS protocol (three pulses at 20 Hz every 2 s; 4500 pulses per session at 150% rMT; twice per week per side to the motor cortex bilaterally). Monkeys Ah and Sa, serving as controls, underwent subhemisection and rehabilitation without rTMS. Monkeys Ah, Sa, and Mi were sacrificed 3.5 months post-SCI, monkeys Da and Mo at

1.5 months, and monkey Ko at 5.5 months. Our findings indicate that while the task success rate did not recover in controls (Ah and Sa), all monkeys receiving rTMS exhibited recovery of grasping function within 1.5 months post-injury. Task success rate rapidly improved to over 90% and was accompanied by reduced grasping time. Compared with task performance during the initial 1.5 months post-SCI, monkey Ko demonstrated more precise pinching later. We also recorded muscle twitches evoked by rTMS throughout recovery. Twitches in distal muscles of the affected forelimb evoked by contralateral motor cortex stimulation were absent after SCI but reappeared in parallel with behavioral recovery. We injected a viral tracer into the contralesional motor cortex to label the CST in each monkey. In monkeys receiving rTMS, labeled CST fibers bypassed the lesion site and projected to lamina IX of the ipsilesional C8 gray matter. Quantitative analysis confirmed that the relative number of such CST fibers in monkeys receiving rTMS was significantly greater than that in controls. In conclusion, we developed a noninvasive rTMS protocol that facilitates motor functional recovery after severe SCI in macaques. rTMS promotes rapid corticospinal plasticity and accelerates restoration of motor output, which may contribute to the recovery of dexterous grasping. Our results highlight the therapeutic potential of rTMS as a clinically translatable strategy for promoting functional recovery after SCI.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Title: An Implantable Intramuscular Electrode Interface for Phase-Dependent Neuromodulation of Locomotor Circuits After Spinal Cord Injury in Freely Moving Mice

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Abstract: Recovery after spinal cord injury depends on activity-dependent plasticity within spared descending pathways, propriospinal networks, and spinal sensorimotor circuits. Precisely timed stimulation may help engage these residual circuits, but mechanistic studies in mice

require stable approaches for recording motor activity and delivering stimulation during ongoing locomotion. Building on our real-time closed-loop neuromodulation platform for spinal cord-injured mice, we developed a compact implantable electrode interface that enables synchronized electromyographic recording, behavioral tracking, and electrical stimulation in freely moving animals.
Using treadmill locomotion with synchronized EMG and high-speed video recording, we evaluated whether endogenous locomotor signals could be used to drive phase-dependent neuromodulation after SCI. Forelimb EMG activity associated with stance onset was used as a real-time marker of locomotor phase to trigger hindlimb stimulation. This closed-loop stimulation reliably evoked hindlimb muscle responses, demonstrating that spared motor signals can be used to coordinate activation of caudal motor circuits after injury. This implantable EMG-based platform provides a framework for studying interlimb coordination, spinal excitability, and activity-dependent circuit plasticity after SCI, while supporting future development of phase-specific neuromodulation strategies in mouse models.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Program #/Poster #: PSTR269.09/AA15

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Reconstruction mechanism of multi-target neural circuit modulation in spinal cord injury

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Abstract: Background & Aims: Motor dysfunction after spinal cord injury (SCI) remains challenging. Single-target neuromodulation has limited efficacy. This study investigated neural circuits magnetic stimulation (NC-MS) based on sensorimotor circuit modulation for motor rehabilitation in SCI rats and its neural plasticity mechanisms. **Methods:** Adult male SD rats with T10 clip-compression SCI were divided into sham, sham stimulation, NRMS (L5-L6 spinal root stimulation), and NC-MS (motor cortex + NRMS) groups. Behavioral tests, electrophysiology, histopathology, multimodal MRI, and single-cell transcriptomics were performed. **Results:** NC-MS improved hindlimb motor function, neural conduction, and neuromuscular activity most effectively. At the spinal cord level, NC-MS reduced tissue damage, enhanced dendritic complexity and spine density, alleviated ultrastructural abnormalities, regulated synaptic plasticity and inflammatory markers, and improved white matter

microstructure. At the cortical level, NC-MS altered functional connectivity and neurotransmitter metabolism. Single-cell sequencing revealed microglial and neuronal subtypes. **Conclusion:** NC-MS promotes motor rehabilitation after SCI, with superior effects to single-root stimulation, by improving neural conduction, spinal cord pathology, synaptic plasticity, inflammation, and sensorimotor cortical connectivity/neurotransmitters.

Disclosures: D. Xu: A. Employment/Salary (full or part-time):; Shanghai University of Traditional Chinese Medicine, Department of Rehabilitation Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western. **L. Cao:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Title: Somatosensory micro-ECoG responses in rats with spinal cord injury and after peripheral transcutaneous neuromodulation

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Abstract: Understanding plasticity of the sensorimotor pathways in spinal cord injury (SCI) is important to develop new methods for neuromodulation (NM) therapies. This study involves μECoG recordings from the rat primary somatosensory cortex (S1HL) under anesthesia. Tactile and proprioceptive inputs were applied by sinusoidal (5, 40, 250 Hz) mechanical stimulation of the hind paw glabrous skin (0.1-0.5 mm) and the exposed gastrocnemius muscle after dissection (0.3-2.7 mm). The subject groups were sham-operated (SO), SCI, NM-sham-operated (NM-SO), and NM-SCI. They were tested at different endpoints (D1-D60) post-op (T8-T9 laminectomy). Contusion-type SCI was induced with an impactor to produce moderate-to-severe injury as verified by the Basso, Beattie and Bresnahan (BBB) locomotor rating scale. NM was administered by transcutaneous and bilateral electrical stimulation of the distal tibial nerve (pulse width: 0.3 ms, frequency: 2 Hz, amplitude: 2 × motor threshold, duration: 30 min. at 3 days/week). The recovery was assessed by withdrawal-reflex thresholds, BBB scores, gait parameters during platform walking, and bladder function. According to a larger cohort in our

laboratory, rats with SCI spontaneously recovered to average BBB scores of 8.0±2.6 after injury (0.2±0.1). The recovery was significantly higher (17.5±2.5) with NM. Facilitatory effects of NM were observed on the withdrawal-reflex thresholds and bladder function, but not much on the gait. For contralateral tactile and proprioceptive inputs, cortical evoked potentials (EPs) were significantly suppressed in the SCI group. However, NM significantly increased the responses to both modalities in the injured rats, almost reaching the sham-operated groups' levels for the proprioceptive inputs. Interestingly, tactile responses in the NM-SO group were higher than those in the SO group suggesting some hypersensitivity. EP latencies were mostly affected by the contralateral proprioceptive inputs. As expected, the latencies increased in injured rats; however, NM did not reverse that. Overall, the μECoG recordings and the locomotor findings show that peripheral NM causes a significant reorganization of the sensorimotor pathways, probably via spinal interneurons, to partially compensate for the loss of function after SCI. Further improvements may be possible by spatiotemporal patterning of the NM based on locomotor activity. Additionally, the perceptual outcome of the plasticity observed in S1HL remains to be tested in awake rats recovering from SCI.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

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Program #/Poster #: PSTR269.11/AA17

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH T32 NS 900467
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Title: Spinal Cord Injury Alters Serotonergic Modulation of Inhibitory Interneurons Regulating Proprioceptive Afferents

Authors: *C. WEST, K. J. DOUGHERTY;
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Abstract: Sensory stimuli constantly enters the spinal cord via sensory afferents. Sensory information is precisely filtered to allow sensory and motor circuits to function properly. Afferent transmission is regulated by GABAergic interneurons (INs) which release GABA onto afferents to produce primary afferent depolarization (PAD). RORβ INs are a subpopulation of GABAergic INs that produces PAD in proprioceptive afferents. The descending activation of RORβ INs and PAD is disrupted after spinal cord injury (SCI) leading to abnormal transmission of primary sensory afferents into the spinal cord which can cause hyperreflexia and spasticity.

Serotonin is a prominent spinal neuromodulator that exerts general facilitation of locomotion and inhibition of sensory systems, in part by modulating afferent transmission. Serotonin both directly inhibits afferent synaptic transmission and modulates inhibitory INs producing PAD. While the direct actions of serotonin on sensory afferents are well studied, serotonergic modulation of PAD-producing inhibitory INs is unclear. Additionally, serotonin receptor plasticity after SCI has been documented in spinal excitatory INs and motor neurons, but whether SCI causes similar plasticity in RORβ INs is unknown. An understanding of if/how the response to serotonin changes in spinal INs that regulate afferent transmission will inform future studies to design serotonergic therapies that target sensory and motor circuits collectively. In this study, we aim to determine how SCI affects serotonergic modulation of RORβ INs. We performed severe T8/9 midline contusion injuries on adult male and female RORβcre; R26-lsl-tdTomato mice. Four weeks later, we performed whole cell patch clamp recordings from RORβ INs in spinal slices from uninjured and SCI mice. We measured passive and active intrinsic properties of RORβ INs at baseline and in response to 0.1μM and 10μM serotonin. In RORβ INs from uninjured mice, the effects of serotonin were concentration dependent, with 0.1μM hyperpolarizing the INs, and 10μM depolarizing INs and increasing action potential firing. RORβ INs from SCI mice were also hyperpolarized in response to 0.1μM serotonin. Although 10μM serotonin depolarized a subset of RORβ INs from SCI mice, the majority were hyperpolarized by serotonin concentrations that depolarized nearly all RORβ INs from uninjured mice. Our findings indicate that SCI induces plasticity in the response of RORβ INs to serotonin, likely due to changes in receptor expression. Plasticity in serotonergic modulation of PAD-producing RORβ INs may contribute to reduced afferent regulation and hyperreflexia after SCI.

Disclosures: C. West: None. **K.J. Dougherty:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

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Title: Behavior-specific dorsolateral striatal dopamine transients are reorganized across recovery from spinal cord injury

Authors: *J. T. EISDORFER, B. DANISH, M. PHU, T. KOWALSKI, R. WANG, D. G. YILMAZ, A. M. MARTINEZ, M. TISCHFIELD, V. E. ABRAIRA;
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Abstract: Recovery from spinal cord injury (SCI) requires relearning how to move, yet which compensatory behaviors are reinforced and the circuits that govern this selection remain unknown. The dorsolateral striatum (DLS) consolidates learned motor routines through nigrostriatal dopamine (DA) input and DLS DA transients strengthen with repeated motor actions. Despite this role, the DLS has never been examined after SCI. We hypothesized that DLS DA acts as a "behavioral gatekeeper" after injury, selectively reinforcing the movements that re-emerge during recovery. To test this, we delivered a moderate T10 contusion SCI to male and female mice expressing the genetically encoded DA sensor GRAB-DA2m in the DLS and recorded DA dynamics longitudinally with fiber photometry across spontaneous recovery. We synchronized DA signals with unsupervised behavioral classification (Motion Sequencing, MoSeq) to align transients to specific, reusable motor motifs ("syllables"), and used AAV-based synaptic labeling to map substantia nigra pars compacta (SNc)-to-DLS input before and after injury. Anatomical tracing showed that nigrostriatal input to the DLS persists after SCI, indicating the circuit remains structurally intact and available for plasticity. Functionally, DLS DA transients were behavior-specific and time-locked to movement onset. The timing and magnitude of these behavior-aligned transients were reorganized across injury and recovery: signals were strongest and most sharply onset-locked in uninjured animals, blunted or absent during paralysis, and re-emerged with altered, often delayed dynamics as animals regained function. In parallel, the entropy of behavioral sequences increased over the course of recovery, tracking the evolving DA dynamics. These data provide the first description of DLS DA signaling after SCI and show that behavior-specific DA transients are reorganized across functional recovery. This positions nigrostriatal DA as a candidate reinforcement signal that shapes which movements return after injury and defines a new class of circuit-level targets for SCI rehabilitation.

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Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

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Title: Enhanced sensorimotor cortex responsiveness to nonplegic hand stimulation and motor network assembly during recovery after spinal cord injury in primates

Authors: *T. TOHYAMA[1,2], R. YAMAGUCHI[3,4], N. GODA[1,5,6], T. YAMAMOTO[1,5,7], N. SADATO[5,7,8], T. ISA[3,4,5,9], M. FUKUNAGA[1,5,6];
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Abstract: Previous studies have reported changes in cortical responses to stimulation of the plegic or nonplegic hand after unilateral neuronal injury. However, whether these changes in cortical responsiveness contribute to central sensorimotor reorganization and recovery of hand movement after injury remains unclear. One of the graph-analytic measures, eigenvector centrality, has been introduced to resting-state functional MRI (fMRI) connectivity over the past decade. Eigenvector centrality quantifies the relative importance of regions of interest (ROIs) by weighting connections to other highly central nodes, likely capturing the hierarchical organization of the connectome and the underlying network assembly. We aimed to investigate the relationships between changes in cortical responsiveness, motor network assembly, and functional recovery after unilateral spinal cord injury. Five macaque monkeys underwent lower cervical cord subhemisection surgery. Hand grasping movements were assessed behaviorally, and longitudinal fMRI was performed under anesthesia to assess responses to tactile stimulation of each hand and resting-state connectivity. Eigenvector centrality was computed from resting-state fMRI data to examine network assembly. Correlations between task-based responses and eigenvector centrality of sensorimotor areas or grasping task performance were examined using ROI and voxel-wise analyses. Following severe paralysis of the ipsilesional hand, four monkeys showed recovery of grasping movements, with an average success rate improving until 16 weeks post-injury. Bilateral sensorimotor hand areas exhibited increased responses to contralesional (nonplegic hand) stimulation at 2-5 weeks post-injury, which declined over time. ROI analyses revealed that these changes in responsiveness were correlated with the centrality of the bilateral premotor cortices and supplementary motor areas, but not with that of the primary motor cortices. An inverse voxel-wise correlation between responses in the ipsilesional sensorimotor cortex and success rates was observed in the four monkeys with good recovery. By contrast, the

monkey with poor recovery exhibited a significant inverse correlation cluster extending extensively across the temporal, parietal, and occipital cortices. These findings suggest that cortical responsiveness enhancement may be caused by post-injury disinhibitory mechanisms involving motor network assembly. Our results indicate that disinhibitory mechanisms can drive large-scale sensorimotor reorganization, and disinhibition reduction leads to long-term recovery after spinal cord injury in primates.

Disclosures: T. Tohyama: None. **R. Yamaguchi:** None. **N. Goda:** None. **T. Yamamoto:** None. **N. Sadato:** None. **T. Isa:** None. **M. Fukunaga:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.14/AA20

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Whole-Brain Mapping of Resting Cerebral Glucose Metabolism Following Hemicontusive Cervical Spinal Cord Injury in Mice

Authors: Z. WANG[1], ***C. DANILOV**[2], D. SETIYA[2], D. P. HOLSCHNEIDER[3];
[1]Psychiatry & Behavioral Sci., Univ. of Southern California, Los Angeles, CA; [3]Psychiatry & the Behavioral Sci., [2]USC, Los Angeles, CA

Abstract: Spinal cord injury (SCI) disrupts communication between the brain and spinal cord, leading to extensive functional reorganization throughout the brain. In this study, we used high-resolution, voxel-based, whole-brain metabolic mapping using the [^{14}C]-2-deoxyglucose autoradiographic method in adult, female mice to characterize functional brain reorganization during the subacute phase of injury (1-week post-SCI).A right-sided moderate contusive injury at the fifth cervical level (C5) was confirmed by glial fibrillary acidic protein (GFAP) immunohistochemistry. Compared with sham controls, SCI mice exhibited significant motor deficits, as assessed by grip strength and rotarod performance, accompanied by reduced glucose uptake in sensorimotor cortical regions, the basal ganglia, and the thalamus. Metabolic decreases were observed in regions receiving direct spinal input, including the ventral posterolateral thalamic nucleus (VPL), as well as in higher-order sensorimotor regions that receive multi-synaptic afferents, including the primary somatosensory cortex, primary motor cortex and caudate putamen. In contrast, increased glucose uptake was observed in the limbic structures, including the amygdala, nucleus accumbens, lateral septum, and hippocampus, as well as in the cerebellum. Most metabolic changes were bilateral, suggesting extensive functional reorganization of ascending and descending neural pathways across both hemispheres. Furthermore, functional metabolic connectivity between the ventral posterolateral thalamic nucleus and primary somatosensory cortex was reduced bilaterally. These preliminary findings demonstrate widespread brain-wide metabolic reorganization during the subacute phase

following a moderate unilateral contusive-type SCI. Whole-brain metabolic mapping provides a valuable framework for identifying neuroplastic adaptations and evaluating the efficacy of emerging therapeutic interventions.

Disclosures: Z. Wang: None. **C. Danilov:** None. **D. Setiya:** None. **D.P. Holschneider:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.15/AA21

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: DFF
DoW (USA)

Title: Activity-dependent mapping of locomotor circuits engaged by neuromodulation after spinal cord injury

Authors: *N. ANTOLIN, R. LEIRAS, O. KIEHN, C. BELLARDITA;
Univ. of Copenhagen, Frederiksberg, Denmark

Abstract: Spinal cord injury (SCI) impairs locomotion by disrupting communication between supraspinal and spinal motor circuits. Despite this disruption, substantial descending pathways often remain anatomically preserved, providing a substrate for neuromodulatory interventions aimed at restoring motor function. Neuromodulation of the cuneiform nucleus (CnF), a key component of the mesencephalic locomotor region, has emerged as a promising strategy to engage these spared circuits. However, the distributed neuronal populations recruited during locomotion and their modulation by SCI and CnF stimulation remain incompletely understood. Here, we combined activity-dependent genetic labeling in TRAP2 mice with quantitative locomotor analyses to identify neuronal ensembles engaged during distinct behavioral conditions. Neurons were permanently labeled during rest, locomotion, or locomotion paired with optogenetic stimulation of the CnF, enabling the discrimination of locomotion-related and stimulation-associated neuronal recruitment patterns. This approach was applied in both intact mice and mice with thoracic incomplete SCI to capture activity-defined populations across supraspinal and spinal locomotor networks.
Together, this work establishes a circuit-level anatomical framework that enables future causal and mechanistic interrogation of activity-defined locomotor circuits, providing a foundation for mechanism-guided neuromodulatory rehabilitation strategies after SCI.

Disclosures: N. Antolin: None. **R. Leiras:** None. **O. Kiehn:** None. **C. Bellardita:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.16/AA22

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH R01NS105725
NIH R01NS136711
NIH S10OD036432
NYS Department of Health C38326GG
Craig H. Neilsen Foundation 998694

Title: Defining the role of M1 intracortical neurons in rehabilitation-mediated functional recovery after spinal cord injury using a novel kinematic deviation index

Authors: P. TALLA[1], X. GUAN[2], A. BERNSTEIN[2], M. SOLIMAN[3], *E. R. HOLLIS[2]; [1]Horace Greeley High Sch., Chappaqua, NY; [2]Neurolog. Surgery, Weill Cornell Med., New York, NY; [3]Burke Neurolog. Inst., White Plains, NY

Abstract: Restoring fine motor skills of the arm and hand is a top priority for individuals living with tetraplegia from spinal cord injury (SCI). Limited relevant clinical interventions exist, thereby necessitating research into mechanisms that can support functional recovery and improve clinical outcomes. Studies in animal models have demonstrated that rehabilitation on skilled forelimb behavioral tasks results in plastic changes within the motor cortex, as areas originally devoted to hindlimb movements play new roles in forelimb control. We propose that intracortical neurons spanning between the forelimb and hindlimb motor cortices facilitate intracortical reorganization underlying skilled forelimb functional recovery. To assess quantitative movement changes, we applied a novel Kinematic Deviation Index (KDI) approach that uses AI-marked spatiotemporal coordinates in recordings of forelimb movements during the single-pellet reaching task (Torres-Espín, 2025), to comprehensively analyze trajectory deviations from healthy movement patterns. An increase in KDI indicates a decline in movement quality. KDI addresses deficiencies in traditional success-rate metrics by assessing compensatory functional strategies. To test the role of intracortical motor circuits in recovery after SCI, we combined a cervical level 5 dorsal column lesion model in C57BL/6J mice with an intersectional optogenetic viral strategy: retrograde transduction with AAV2retro-Cre and Cre-dependent inhibitory opsin (GtACR2) expression to selectively silence intracortical neurons. Among 954 experimental trials ($n = 7$) and 765 control trials ($n = 6$), we KDI was used to discriminate between three reach outcomes: successful pellet recovery, unsuccessful, and attempted reaches (estimated marginal means, pairwise contrast: KDI increase from successful, to unsuccessful, to attempted reaches ($p < 0.0001$)); KDI sensitivity to SCI model (baseline to post-SCI increase; $p < 0.001$); and optogenetic silencing-induced movement quality changes pre-injury (significant increase ($p < 0.05$)) and post-rehabilitation (non-significant change). We found that silencing existing intracortical circuits disrupted movements in intact animals and impaired successful reach performance but silencing those same circuits post-rehabilitation had a much more limited effect.

This indicates that neuroplastic mechanisms may be reshaping the circuits facilitating skilled movement coordination during rehabilitation. Our findings on circuit plasticity and validation of the KDI as a reliable analytic tool will promote more robust SCI research and optimized rehabilitation therapies.

Disclosures: P. Talla: None. **X. Guan:** None. **A. Bernstein:** None. **M. Soliman:** None. **E.R. Hollis:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.17/AA23

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NS132773

Title: Growth Pathway Activation Drives Maladaptive Plasticity After Spinal Cord Injury

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Abstract: Reactivating intrinsic growth programs is a central strategy for promoting recovery after spinal cord injury (SCI). PTEN suppression activates growth pathways and promotes axonal growth, yet its long-term behavioral consequences remain poorly understood. Using AAV-retro delivery in a cervical SCI mouse model, we show that PTEN deletion drives significant transcript loss in corticospinal neurons but fails to restore coordinated motor function. Instead, PTEN-deleted animals develop a progressive maladaptive phenotype resembling sensory complications in SCI patients, including scratching, licking, and ulcer formation, quantified longitudinally using AI-assisted behavioral analysis. Structurally, 3D lightsheet microscopy data suggest increased CST sprouting in PTEN-deleted animals, consistent with aberrant circuit remodeling underlying these behaviors. These findings challenge the assumption that more growth is always beneficial, positioning this model as a platform to dissect the circuit mechanisms underlying maladaptive plasticity after SCI.

Disclosures: M. Metcalfe: None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.18/AA24

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: ANR-21-CE16-0007
Wings For Life - 2023_058

Title: Plasticity of medullary descending pathways after spinal cord injury and trans-spinal magnetic stimulation

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Abstract: Various neuronal populations in the brainstem, particularly the medulla, are crucial for controlling distinct aspects of movement, including posture and locomotion. Despite the known potential plasticity of descending medullary pathways after spinal cord injury (SCI), the exact nature, functional implications, and modulation of such plasticity by therapeutic approaches remain unclear. We explore here, in a mouse SCI model of thoracic hemisection, the comparative plasticity of specific subtypes of descending medullary neurons and the impact of a non-invasive therapy, repetitive trans-spinal magnetic stimulation (rTSMS). Expectedly, retrograde tracing revealed a marked reduction in the number of ipsilateral labeled medullary neurons following thoracic hemisection, while the contralateral ones were largely preserved. Subtype-specific analyses, however, demonstrated distinct responses to injury among medullary populations, notably with respect to their innervation of the ipsilateral and contralateral spinal cord. Importantly, a 14-day rTSMS treatment improved recovery, both anatomically and functionally. Indeed, we observed changes in the organization and distribution of specific medullary projections in the spinal cord, suggesting the modulation of plasticity in selective pathways. Functionally, rTSMS significantly improved the recovery of skilled, adaptative locomotion. These findings refine our understanding of plasticity in descending medullary pathways after SCI, and identify this plasticity as one potential underpinning of the rehabilitative effects of neuromodulatory therapies.

Disclosures: P. del Cerro de Pablo: None. **L. Moncomble:** None. **A. Lamour:** None. **A. Heuzé:** None. **N. Guerout:** None. **J. Bouvier:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.19/AA25

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Mary Tucker Currie Endowment To JWG

Title: Proprioceptive protection: limb position gates the acute effects of nociceptive stimulation, but may not produce lasting metaplastic benefits comparable to controllable stimulation.

Authors: *N. ROTTER, K. E. HUDSON, P. CHANDRAMOHAN, C. T. PHINNEY, K. N. COLPITTS, J. W. GRAU;
Texas A&M Univ., College Station, TX

Abstract: Prior work has shown that animals can learn to maintain hind limb flexion after communication with the brain has been interrupted by means of a thoracic (T2) transection. In these experiments, T2 transected rats are placed in a Plexiglas tube with their hind legs hanging freely below. A 7-cm rod (contact electrode) is taped to the rat's paw and a flexion response is elicited by applying electrical stimulation (shock) to the tibialis anterior muscle. Rats given shock whenever the contact electrode touches an underlying salt solution learn to maintain the leg in a flexed position. Animals that are experimentally coupled (yoked) to rats with behavioral control (master) do not learn and exhibit a lasting learning impairment (a form of maladaptive plasticity). Just 6 min of uncontrollable stimulation undermines subsequent learning. Training with controllable stimulation also enables learning when animals are later tested on the opposite leg with a higher response criterion (achieved by raising the level of the salt solution) and has a protective effect that counters the adverse effect of uncontrollable stimulation [a kind of plasticity of plasticity (metaplasticity)].
Other work has shown that limb position at the time of shock exposure modulates the induction of the deficit; animals exposed to 6 min of intermittent shock do not exhibit a learning impairment if the limb is maintained in a flexed position. Here we show that this remains true when animals are given an extended (30 min) exposure to intermittent shock. Additional studies are examining whether this treatment has a metaplastic effect. Spinally transected rats were exposed to intermittent shock for 30 min while the leg was maintained in a flexed position. When tested on the opposite leg with a higher criterion, they failed to learn. Further work is being conducted to test whether the treatment engages a protective effect that counters the development of the learning impairment. The results suggest that leg position gates the acute consequences of noxious stimulation, but may not have a metaplastic effect comparable to that produced by controllable stimulation.

Disclosures: N. Rotter: None. **K.E. Hudson:** None. **P. Chandramohan:** None. **C.T. Phinney:** None. **K.N. Colpitts:** None. **J.W. Grau:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.20/AA26

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Translational Models Of Neuroplasticity: Evaluating Functional Recovery Trajectories and Biomechanical Outcomes Following Multimodal Neurorehabilitation in a Canine Spinal Cord Injury Cohort

Authors: *D. SRINIVASAN[1], B. LEMUS[2], G. ARIAS[2];
[1]High Tech. High North County, San Marcos, CA; [2]Companion Animal Hlth. and Rehabil. Ctr., Escondido, CA

Abstract: Spinal cord injury (SCI) and associated neurodegeneration present complex challenges for functional motor recovery, requiring evaluation of combinatorial therapies. This retrospective comparative study utilized a naturally occurring canine model of spinal cord dysfunction—including intervertebral disc disease (IVDD), fibrocartilaginous embolism (FCE), and chronic myelopathy—to investigate the efficacy of multimodal neurorehabilitation on spinal cord plasticity and locomotor restoration. Serial neurofunctional exams, goniometric range-of-motion, and biomechanical limb-loading assessments were evaluated across 18 client-owned dogs undergoing integrative neurorehabilitation (hydrotherapy, photobiomodulation, acupuncture, shockwave therapy, and targeted exercises). To standardize heterogeneous baseline deficits, a retrospective Rehabilitation Outcome Severity Index (ROSI) was implemented. Trend analyses revealed that 77.8% (14/18) of the cohort demonstrated significant improvements in neurological status and functional mobility. Locomotor recovery was most pronounced in acute post-decompressive hemilaminectomy and ischemic FCE models, with 66.7% (4/6) of severely affected, non-ambulatory subjects regaining independent, coordinated quadrupedal ambulation within a mean window of 6.2 weeks. Longitudinal mobility scores showed robust statistically significant improvement between intake and final follow-up (paired comparison, $p<0.001$). Conversely, subjects with chronic, profound spinal cord compromise and absent deep nociception exhibited limited functional reorganization. Biomechanical data confirmed significant improvements in stance symmetry, pelvic limb weight-bearing distribution, and neuromotor coordination across the responsive cohort. These findings highlight the utility of naturally occurring large-animal models for translational SCI research and demonstrate that multimodal neurorehabilitation effectively drives functional recovery.

Disclosures: D. Srinivasan: None. **B. Lemus:** None. **G. Arias:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.21/AA27

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: PA Spinal Cord Injury Research Grant SAP# 4100098597

Title: Using Downhill Training to Improve Gait Stability and Efficiency in a Rodent Contusive Spinal Cord Injury

Authors: K. J. DAMM, H. E. DALTON, ***L. R. MONTGOMERY**;
Physical Therapy and Rehabil. Sci., Drexel Univ., Philadelphia, PA

Abstract: Rationale: The proportion of people with incomplete spinal cord injury (SCI) has increased in the last decade. Many can walk at home but have limited community ambulation due to decreased gait efficiency and gait instability in early stance. Walking aids increase stability but decrease walking speed/efficiency and provide barriers to walking in narrow spaces and complex environments. Thus, many individuals with SCI who are able to walk will continue to limit their participation in community activities. During gait the period which is important for stability and gait efficiency is in early stance during weight acceptance or yield. After SCI this period of gait is often disrupted and there are still few ways to address this in rehabilitation. Devising new rehabilitative interventions and strategies to improve stability and efficiency in early stance is vital to increase independence and quality of life in individuals with incomplete SCI. One intervention that we are implementing in SCI rehabilitation is downhill walking which requires increased neuromuscular control in early stance. Due to the emphasis on this period of gait during downhill walking, it is positioned as a novel intervention which could improve gait efficiency and stability, ultimately leading to greater independence and community engagement in individuals with SCI. Design/Methods: Adult, female Wistar rats were trained to walk on level and declined surfaces. Hindlimb kinematic data was collected preSCI on 0° (level), -10°, and -20°. Following a mid-thoracic contusion (175 kdyn) rats were randomly assigned to a downhill or non-trained group. At 6wpi data was collected and compared to preSCI and also compared within each time point for the different slopes (0° v -10° v -20°). We found that PreSCI the ankle was more flexed with greater yield in early stance on -20° compared to 0°. PostSCI, downhill trained rats continued to show increased ankle flexion on -20° compared to 0° (12° difference) whereas non-trained showed minimal difference (1°). By adapting to the changing slope, the downhill trained rats were able to continue using strategies to maintain stability and efficiency of gait compared to nontrained rats who limited flexion of the limb to maintain stability at the expense of efficiency Conclusion: These findings suggest that downhill training targets early stance, allowing animals to continue to adapt during early stance when faced with more challenging walking environments. This enabled those animals to continue to use efficient gait mechanisms without compromising stability.

Disclosures: K.J. Damm: None. **H.E. Dalton:** None. **L.R. Montgomery:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.22/AA28

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH NINDS K99NS144632
NJCSCR CSCR26ERG007
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NIH NINDS K01NS116224
NJCSCR CSCR26IRG011
NIH NINDS T32NS115700

Title: Treadmill step training promotes corticospinal tract plasticity after incomplete spinal cord injury

Authors: *B. DANISH[1], M. PHU[5], J. EISDORFER[1], T. KOWALSKI[2], A. M. MARTINEZ[3], R. WANG[4], D. G. YILMAZ[4], M. TISCHFIELD[1], V. E. ABRAIRA[6];
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Abstract: Spinal cord injury (SCI) often impairs motor functions such as voluntary movement and fine motor control, with the corticospinal tract (CST) being a crucial pathway affected. While CST-targeted rehabilitation, such as treadmill training, supports motor recovery, gaps remain in understanding the topographical changes within the CST and how they correlate with behavioral outcomes. In this study, we utilized a custom Emx1Cre;LSL-SynGFP mouse line to quantify CST plasticity following moderate contusion SCI, both with and without exercise (treadmill) training. Fluorescent labeling of cortical synapses allowed for detailed visualization of descending CST rewiring, and we assessed its relationship to behavioral outcomes, including kinematics analysis and motivational state. Mice were stratified by motivational state using the Progressive Ratio Assay, and locomotor recovery was evaluated through the Basso Mouse Scale (BMS), joint/limb kinematics, and Motion Sequencing (MoSeq) analysis. Our findings indicate that treadmill training enhances CST rewiring, especially in highly motivated animals, leading to increased synaptic density in the ventral horn and improved BMS subscores. Motivation further influenced specific kinematic parameters, such as toe clearance, while treadmill training significantly improved speed by reducing the stance phase. Results suggest that while treadmill training induces broad beneficial outcomes, motivation may fine-tune recovery, influencing neural circuit and behavioral changes. This suggests multiple mechanisms converge to promote recovery—those we cannot control and those we can. These results underscore the combined role of task-specific training and also perhaps motivation in driving CST plasticity and functional recovery after SCI.

Disclosures: B. Danish: None. **M. Phu:** None. **J. Eisdorfer:** None. **T. Kowalski:** None. **A.M. Martinez:** None. **R. Wang:** None. **D.G. Yilmaz:** None. **M. Tischfield:** None. **V.E. Abraira:** None.

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.23/AA29

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Novel Chronic Sacral Spinal Cord Injury Model in Cynomolgus Monkeys

Authors: *V. P. RUTH[1], R. NISHIKATA[2], T. HAMASAKI[2], M. TANOUE[3], Y. HORIMOTO[2], S. TOKUYOSHI[3], K. HAYASHIDA[2];
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Abstract: There is currently no established non-human primate (NHP) model of chronic spinal cord injury (SCI) that has high translational relevance to human SCI with minimal effect on quality of life (QOL) of animals. The present study aimed to develop a chronic SCI model in three female cynomolgus monkeys (aged 3-5 years) that preserves animal QOL compared to traditional SCI models, while enabling longitudinal evaluation of withdrawal response following compression injury to the sacral spinal cord. SCI was induced by inflating a balloon catheter in the epidural space for 1 hour at a target location between the L3-L4 vertebrae, below the lumbar enlargement of the spinal cord. Pre- and post-lesion withdrawal response in the tail and baseline activity in the home cage were evaluated for up to 8 weeks post-injury with electromyographic (EMG) recordings by a transmitter implanted into the left and right quadriceps femoris and flexor caudae longus or brevis. Although the study is currently ongoing, all animals have demonstrated a consistent lack of tail withdrawal response at weekly assessments after injury. In the first animal, cumulative EMG activity in the tail decreased by ≥92.2% compared with baseline and remained below 10% of baseline levels for 6 weeks post-SCI. A similar reduction in motor activity was observed in the second animal for 3 weeks post-injury. Selective tail paralysis was observed immediately after SCI in all animals and was maintained into the sub-acute or chronic phase. During general observations, no impairments in bowel, bladder, or hindlimb function, nor any significant body weight loss, were reported. The current model resulted in selective paralysis to the tail of cynomolgus monkeys, enabling evaluation of sacral SCI into the chronic phase without sacrificing QOL of animals. These results warrant further investigation into glial scar formation and spinal cord histopathology, longitudinal MRI assessments at defined time points, and refinement of methodologies, including spinal reflex evaluation.

Disclosures: V.P. Ruth: A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **R. Nishikata:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **T. Hamasaki:** A. Employment/Salary (full or part-time):; Shin Nippon Biomed. Laboratories, Ltd. **M. Tanoue:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **Y. Horimoto:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **S. tokuyoshi:** A. Employment/Salary (full or part-

time):; Shin Nippon Biomedical Laboratories, Ltd. **K. hayashida:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd..

Poster

PSTR269: Spinal Cord Injury: Electrical Stimulation, Neuromodulation, Rehabilitation, and Circuits: Animal Studies

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR269.24/AA30

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Bioelectronics and Nanomedicine Research Center
Spinal Cord and Brain Injury Research Center Pilot Award
UKNeu-PREP R25-NS130963
Kentucky Spinal Cord and Head Injury Research Trust Grant 24-6

Title: The Characterization of a Heterogeneous Rat Model of Degenerative Cervical Myelopathy

Authors: *J. MOSES[1], C. C. WOLSH[3], M. KYWERIGA[4], J. C. GENSEL[2], W. BAILEY[1], F. FARHADI[1];
[2]Physiology; Spinal Cord and Brain Injury Res. Ctr., [1]Univ. of Kentucky, Lexington, KY; [3]Physiol., Univ. of Kentucky, Col. of Medicine, Dept. of Physiology, Spinal Cord and Brain Injury Res. Ctr., Lexington, KY; [4]Preclinical program, Novoron Biosci., San Diego, CA

Abstract: Degenerative Cervical Myelopathy (DCM) is the leading cause of non-traumatic Spinal Cord Injury (SCI) affecting about 2% of the global population and 5% of the population above 40 years of age. This form of SCI results from chronic compression of the cervical spinal cord, leading to progressive degeneration, and is diagnosed by MRI demonstrating cord compression with possible myelomalacia. In both preclinical and clinical studies, evidence suggests that inflammatory responses and functional capacity change as DCM progresses. However, we lack a clear framework linking changes in symptoms and function to biological and structural markers of disease progression. This gap limits the exploration of possible therapeutic interventions that can be implemented prior to decompression surgery. We hypothesize that the trajectory of disease severity can be identified through multivariate analysis of functional decline and changes in biological outcomes as DCM progresses. In this study we used a screw and nut DCM model in female Sprague-Dawley rats to induce chronic compression and produced two groups of animals. One group represented a surgical sham and the other received gradual compression. Animals underwent behavioral testing to track functional deficits in dexterity, proprioception, balance, and thermal sensitivity from the onset of compression through the chronic time point. Animals also underwent weekly MRIs to analyze the changes in tissue structure as the compression progresses to the chronic timepoint. Finally at the chronic timepoint, animals were sacrificed and tissue and plasma were harvested to analyze changes in immune cell activation and circulating inflammatory serum biomarker concentration between sham and injured animals. Through this project we will correlate functional and biological

outcomes to develop a sensitive scoring system for DCM in rats that efficiently serves as a wholistic summation of severity. These findings will establish how individual symptoms, analyzed as correlates, can assess overall disease severity.

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Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.01/AA31

Topic: E.01. Somatosensation – Pain and Itch

Title: Nociceptive modulation by inactivation of TRPA1 and TRPV1 channels

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Abstract: Pain is a necessary alert signal that sets off protective responses. Painful stimulation of peripheral receptors triggers a cascade of nociceptive signaling along ascending somatosensory pathways. Transient receptor potential (TRPA1 and TRPV1) channels are involved in pain and itch sensations, making them attractive therapeutic targets. Here, we aimed to investigate pungent nociceptive substances, cinnamon aldehyde (CA), allyl isothiocyanate (AITC, the main compound of mustard oil), and capsaicin (CAPS) from chili peppers, which elicit thermal hyperalgesia and mechanical allodynia in mice, and studied the potential roles of TRP channels in pain modulation. The experiments were conducted in male C57BL/6J mice purchased from Jackson Laboratories, with a body weight of < 50 g. We measured nociceptive thermal paw withdrawal latencies (Hargreaves test) and mechanical thresholds (electronic von Frey test) bilaterally in mice at various time points following plantar applications of CA, AITC, and CAPS, which produced thermal hyperalgesia and mechanical allodynia. When pretreated with the TRPA1 antagonist (HC-030031), we observed a significant reduction in these pain behavioral responses to AITC and CA applications. Pretreatment with the TRPV1 antagonist (capsazepine) produced significant attenuation of thermal hyperalgesia and mechanical allodynia evoked by two doses of CAPS. We thus showed that noxious chemical irritants eliciting thermal hyperalgesia and mechanical allodynia are mediated via the activation of TRPA1 and TRPV1 cation channels. The current study confirms that chemical irritants (AITC, CA, and CAPS) elicited thermal hyperalgesia and mechanical allodynia via the activation of TRP channels. This hyperalgesia and allodynia were attenuated by the TRPA1 channel antagonist HC-030031 and the TRPV1 channel antagonist capsazepine. Our findings indicate that these thermo- and

mechanosensitive ion channels are capable of signaling temperature and mechanical changes across the range normally encountered in the environment. The discovery of dual antagonists that simultaneously target both TRPA1 and TRPV1 channels will represent a new and promising therapeutic approach for pain treatment.

Disclosures: M.G. Tsagareli: None. **I. Nozadze:** None. **G. Gurtskaia:** None. **M. Tsagareli:** None. **M. Iodi Carstens:** None. **G. Gedevanishvili:** None. **E.E. Carstens:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.02/AA32

Topic: E.01. Somatosensation – Pain and Itch

Support: NCCIH DIR
NINDS DIR
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NINDS HEAL Initiative K99
EMBO Fellowship
NIH OADR Fellowship

Title: Nociceptors use multiple neurotransmitters to drive pain

Authors: *D. I. MACDONALD, R. BALAJI, A. T. CHESLER;
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Abstract: Nociceptors are excitatory neurons that express a range of neuropeptides and have the essential role of detecting noxious mechanical, thermal and chemical stimuli. Ablating these neurons profoundly reduces responses to pain. Here we investigated how nociceptive information is transmitted by developing genetic approaches to suppress glutamate transmission and neuropeptide signaling, individually and in combination. Remarkably, many pain responses persisted in mice where either nociceptor glutamate or neuropeptide signaling was blocked. By contrast, mice lacking both glutamate and neuropeptide transmission in nociceptors displayed profound pain insensitivity closely matching the effects of cell ablation. Together our results establish a role for neuropeptides as bona fide pain transmitters and demonstrate redundancy in nociceptor signaling, resolving long-standing questions about how pain is communicated to the brain.

Disclosures: D.I. MacDonald: None. **R. Balaji:** None. **A.T. Chesler:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.03/BB1

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH 1R01DK134893
NIH 1U19NS130608

Title: Integration of Human Peripheral Ganglia Spatial Transcriptomics Data Identifies Dorsal Root Ganglion-enriched Targets for Pain Therapeutics

Authors: *J. C. YANG[1], N. VARGHESE[2], C. MCKEE[2], R. GUNARATNA[2], M. MANCILLA MORENO[4], M. YOUSUF[4], N. JOSHI[3], R. M. KLEIN[2], R. L. KRAUS[2], D. A. HENZE[2], T. J. PRICE[4], R. CARR, III[1];
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Abstract: A promising emerging strategy for pain mitigation is to reduce the excitability of sensory neurons in the dorsal root ganglion (DRG), which translate peripheral sensations into signals interpretable by the central nervous system. However, given the protein expression profile overlap between DRG and sympathetic ganglion neurons, it is essential to identify DRG-enriched genes to enable selection of targets that avoid undesirable sympathetic effects. Spatial transcriptomics enables investigation of gene expression in barcoded spots mapped onto tissue slices. Methods to integrate multi-slice spatial transcriptomics data are currently not well defined, limiting the ability to compare gene signatures across conditions, tissue types, and patients while retaining histopathological context. We present a comparative analysis between human DRG (n=20 sections, representing 3 female and 6 male donors) and human sympathetic chain ganglia (SCG) (n=12 sections, representing 3 female and 3 male donors) tissues using 10X Visium spatial transcriptomics that also addresses the technical challenges of comparing two tissue types. We performed spot deconvolution using semi-supervised topic models trained on DRG or SCG data to estimate cell-type proportions per spot and assign each spot to the cell type with the maximal proportion. In cross-sectionally cut ganglia slices, these classifications aligned with expected tissue architecture. Repurposing a strategy from single-cell RNA-seq analysis, we summed counts (pseudobulked) across all neuronal spots for each tissue slice prior to performing a comparative analysis of DRG versus SCG neurons. To validate our procedure, we identified known markers of sensory neurons including *TRPV1* and *SCN10A* as DRG-enriched, while known markers of sympathetic neurons including *TH* and *DBH* were SCG-enriched. Our approach establishes a framework for integrating multi-slice spatial transcriptomics data and yields a set of DRG-enriched targets for pain therapeutics.

Disclosures: J.C. Yang: A. Employment/Salary (full or part-time):; Merck & Co., Inc. **N. Varghese:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **C. McKee:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **R. Gunaratna:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. **M. Mancilla Moreno:** None. **M. Yousuf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NuvoNuro. **N. Joshi:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. E. Ownership Interest (stock, stock

options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc. **R.M. Klein:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc. **R.L. Kraus:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc. **D.A. Henze:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc. **T.J. Price:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NuvoNuro, PARMedics, Ted and Greg's, Nervelli. **R. Carr:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck & Co., Inc..

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.04/BB2

Topic: E.01. Somatosensation – Pain and Itch

Support: Craig H. Neilsen Foundation 1165231

Title: Selective inhibition of FABP5 reduces the activity of CaV3 channels in nociceptors and pain hypersensitivity in a mouse model of spinal cord injury.

Authors: J. GUPTA[1], H. LIU[1], K. GUNARATNA[1], M. USMAN[1], M. KACZOCHA[1], ***M. PUOPOLO**[2];
[1]Anesthesiol., [2]Stony Brook Med., Stony Brook, NY

Abstract: Up to 60-70% of spinal cord injury (SCI) patients develop chronic, intractable neuropathic pain (SCI-NP). Previous data from our laboratory showed that SCI induces an increased activity of CaV3 channels which in turn contribute to driving nociceptors' hyperexcitability and the development/maintenance of SCI-NP in rodent models of SCI. The goal of this project is to target FABP5, a component of the endocannabinoid system, to inhibit the activity of CaV3 channels with the aim of reducing nociceptors' hyperexcitability and pain hypersensitivity following SCI. All experiments were performed in SCI and sham mice at 3-5 months post-SCI or post-laminectomy, respectively. SCI was induced by a midline spinal cord contusion at T10. *In vivo*, mechanical allodynia was measured with von Frey filaments using the up-down method with the 50% threshold. Spontaneous pain was measured with the conditioned place preference (CPP) paradigm. For *in vitro* electrophysiology, dorsal root ganglia (DRG) neurons were isolated from SCI and sham mice and incubated with vehicle or 5 μM ART26.12 (FABP5 inhibitor) for 12 hours. In voltage clamp, the action potential clamp technique was used

to measure the interspike CaV3 current (sensitive to 1 μM TTA-P2, a blocker of CaV3 channels). In current clamp, after checking for spontaneous activity, the frequency-current (F-I) relationship was measured by injecting current from 0-1000 pA (50 pA increments) in vehicle and in the presence of 1 μM TTA-P2. The 50% mechanical threshold dropped from 1.37±0.10 g (pre-injury) to 1.03±0.09 g (post-SCI) and to 1.01±0.11 g following vehicle injection. ART26.12 (40 mg/kg i.p.) increased the 50% mechanical threshold to 1.38±0.29 g (n=12) at 1-hour post-injection. In the CPP paradigm, SCI mice showed an increase in preference for the ART26.12 paired chamber (40 mg/kg, i.p.) of 55±24 s and a decrease in preference in the vehicle-paired chamber of -20±19 s (n=12). In SCI-nociceptors, the total interspike calcium charge and the interspike CaV3 charge were reduced from 85±21 fC/pF and 71±21 fC/pF (n=14) in vehicle to 46±12 fC/pF and 16±7 fC/pF (n=15) in ART26.12. The incidence of spontaneous activity of SCI-nociceptors dropped from 56% in vehicle to 31% in ART26.12. While baseline F-I relationships were similar between groups, in SCI-nociceptors incubated with ART26.12 there was little change of the F-I relationship relative to SCI-nociceptors incubated with vehicle. Data are reported as mean±SEM. The data suggest that FABP5 inhibition reduces the activity of CaV3 channels and the incidence of spontaneous activity in nociceptors which we propose underlie the reduced pain hypersensitivity observed in vivo.

Disclosures: J. Gupta: None. **H. Liu:** None. **K. Gunaratna:** None. **M. Usman:** None. **M. Kaczocha:** 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.; Stony Brook Mecine. **M. Puopolo:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.05/BB3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS080889 to MLB

Title: Mineralocorticoid receptor signaling reduces somatostatin expression in developing sensory neurons and drives neonatal pain following early life stress.

Authors: *F. EID[1], E. K. SERAFIN[5], M. MUNIZ[2], S. WOODKE[3], M. L. BACCEI[4]; [2]Res. Innovation in Neurosci. Educ. for Underserved Populations Undergraduate Fellowship, [3]Med. Scientist Training Program, [4]Anesthesiol, [1]Univ. of Cincinnati, Cincinnati, OH; [5]Col. of Med., Cincinnati, OH

Abstract: Early life stress (ELS) causes pain hypersensitivity in neonatal mice and alters the transcriptional profile of the immature dorsal root ganglia (DRG), highlighted by a marked reduction in the expression of a neuropeptide, somatostatin (Sst), which is known to

constitutively suppress peripheral nociceptive transmission during adulthood. However, the mechanisms that drive plasticity in gene expression within the developing DRG and neonatal pain following ELS remain unclear. Here we investigated the degree to which ELS-induced neonatal pain was mediated by corticosterone signaling onto sensory neurons and potential changes in peripheral Sst transmission. The conditional knockout of the mineralocorticoid receptor (MR), but not the glucocorticoid receptor, from immature DRG neurons prevented ELS-evoked neonatal pain. In contrast, the systemic administration of the selective MR antagonist eplerenone failed to acutely influence pain after ELS, thus suggesting that MR activation enhances pain during the neonatal period via canonical effects on gene transcription. Meanwhile, hindpaw injection of the Sst receptor antagonist cyclo-somatostatin increased spontaneous nocifensive behaviors in control pups, but not in pups previously subjected to ELS, raising the possibility that a disruption in tonic anti-nociception mediated by peripheral Sst contributes to neonatal pain following ELS. Furthermore, administration of the peripherally-restricted Sst analog octreotide reversed noxious cold and pressure hypersensitivity in neonatal mice following ELS. Finally, the selective deletion of MR from sensory neurons prevented the ELS-induced decrease in Sst expression. Collectively, these results provide novel mechanistic insight into the effects of chronic early life adversity on nociceptive processing in the developing nervous system.

Disclosures: F. Eid: None. **E.K. Serafin:** None. **M. Muniz:** None. **S. Woodke:** None. **M.L. Baccei:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.06/BB4

Topic: E.01. Somatosensation – Pain and Itch

Support: the Ministry of Internal Affairs and Communications Grant JPMI10001
JSPS KAKENHI Grant number JP24KJ2126

Title: Pain threshold induced by 28-GHz millimeter-wave exposure on human skin

Authors: *A. YUASA[1], S. UEHARA[2], K. USHIZAWA[3], S. KODERA[4], A. HIRATA[5], Y. OTAKA[6];
[1]Fujita Hlth. Univ. Sch. of Hlth. Sci., Aichi, Japan; [2]Dept. of Hlth. Sci., Fujita Hlth. Univ. Sch. of Hlth. Sci., Toyoake / Aichi, Japan; [3]Fujita Hlth. Univ. Sch. of Hlth. Sci., Nagoya/Aichi, Japan; [4]Nagoya Inst. of Technol., Aichi, Japan; [5]Nagoya Inst. of Technol., Nagoya, Japan; [6]Dept. of Rehabil. Med., Fujita Hlth. Univ. Sch. of Med., Aichi, Japan

Abstract: Excessive exposure to millimeter waves may cause pain and tissue damage at exposed body sites. Although the perception of pain may vary depending on the heat source, only a few studies have investigated the pain threshold using millimeter waves in humans. In addition,

thermal perception, including warmth, heat, and pain, is initiated by the activation of transient receptor potential channels, but their overlapping activation ranges make distinct sensory thresholds difficult to define. Furthermore, tingling is known as subjective, qualia-like experience and may also be elicited by non-thermal stimulation. Consequently, the threshold temperature for different sensations during millimeter-wave exposure remains unclear. Here, we investigated the thermal effects of millimeter waves in terms of: (i) temperature-dependent changes in different types of sensations (warmth, heat, tingling, and pain) and their perception thresholds, and (ii) the association of individual physical characteristics on pain perception. Thirty-five healthy adults (mean age, 41.9 years; standard deviation, 13.4; 17 women) were exposed to a 28 GHz millimeter wave on their left middle fingertip at an input power of 8.5 W (incident power density: 1.00 W/cm^2) for up to 10 min. The temperature at which the initial subjective perception of each of the four sensation types occurred was determined as the perception threshold for that sensation. When the skin surface temperature exceeded 44°C or when the participant felt pain, the exposure was terminated. The association between participants' physical characteristics and the presence of pain was investigated using logistic regression analysis. Consequently, the perception thresholds increased in the following order: warmth < heat < tingling < pain. A total of 18 (51% of all) participants perceived pain, and the pain perception threshold was 41.9°C. Univariable analyses showed that sex was significantly associated with pain perception, with women were more likely than men to perceive pain (odds ratio, 4.80 [1.15-20.09], $p = 0.032$), which may be partially explained by sex-related differences in hydration levels and finger circumference. Our findings suggest that sensations tend to be perceived in a sequential manner as the skin surface temperature increases and that a tingling sensation may serve as an early warning sign of impending pain. Importantly, our results demonstrated that exposure to millimeter waves can induce pain at a skin surface temperature of approximately 42°C. Furthermore, our observation revealed clear sex differences in sensitivity to pain perception under millimeter-wave exposure.

Disclosures: A. Yuasa: None. **S. Uehara:** None. **K. Ushizawa:** None. **S. Kodera:** None. **A. Hirata:** None. **Y. Otaka:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.07/BB5

Topic: E.01. Somatosensation – Pain and Itch

Title: Regulation of nociception in a Drosophila melanogaster model by the eIF4F translation initiation complex

Authors: *H. A. CHURCH[1], A. C. BELLEMER[2];
[1]Dept. of Biol., [2]Biol., Appalachian State Univ., Boone, NC

Abstract: Nociception is the process by which potentially harmful environmental stimuli are detected and encoded by the nervous system to generate behavioral responses. This process relies on the function of specialized polymodal sensory neurons in diverse animal taxa. Nociceptors may undergo long-lasting plasticity in response to injury, infection, or inflammation that requires regulation of nociceptor gene expression. One potential source of gene regulation during plasticity is translational control via the eukaryotic initiation factor 4F (eIF4F) complex, which has been determined in some animal models to have an effect on basal nociception and nociceptive hypersensitization. Previous studies have indicated the eIF4A subunit is required for normal thermal nociception in a larval *Drosophila* model, but a comprehensive investigation of eIF4F assembly has not been conducted. In this study, we focus on the regulation of the eIF4E cap-binding protein in nociception, with a specific focus on eIF4E phosphorylation and regulation by other cellular factors. Our preliminary results suggest that eIF4E knockdown and alteration of eIF4E phosphorylation do not have a major effect on baseline nociception, but future studies will focus on how these mechanisms may regulate sensitization of larval nociception following injury. These studies are expected to provide insight into post-transcriptional gene regulatory mechanisms that regulate sensory neuron plasticity in a context that is relevant to chronic pain and human health.

Disclosures: H.A. Church: None. **A.C. Bellemer:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.08/BB6

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 1R21NS12859901

Title: Treating Sustained and Chronic Pain with Genetically Encoded Gq Inhibitors

Authors: *A. DABBS;
Neurosurg., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Sustained and chronic pain affect more than 20% of the U.S. population and are a major driver opioid addiction. Normal, healthy pain is initiated in pain-sensing neurons, the nociceptors, by cation channels that open in response to noxious heat, mechanical stress, or chemical stimuli (TRPV1, PIEZO2, etc.). In contrast, sustained and chronic pain are driven by the integrated effects of numerous ligands acting through multiple expressed G protein–coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) that drive nociceptors toward allodynia (pain without stimulus), hyperalgesia (exaggerated pain), and peripheral sensitization (pain in response to normally benign stimuli). These pathology-driving signals converge on a small number of intracellular G protein mediators, Gq, RAS, and Gs, making them attractive therapeutic targets for the treatment of sustained and chronic pain. However, effective small

molecule inhibitors of Gq, RAS, or Gs cause systemic, intolerable toxicities due to the many roles for these G proteins in nearly all cells and organ systems. Our team is instead developing genetically encoded G protein inhibitors (GEGIs) that block Gq, RAS, and/or Gs signaling. As proof-of-concept we show here that an N-myristoylated peptide from PLCß3 that selectively bind GTP-Gq successfully inhibits Gq signaling in both HEK293 cells and in primary mouse dorsal root ganglion (DRG) neurons. Moreover, delivery of these genetically encoded Gq inhibitors (**GEGqIs**) into mouse DRG neurons in vivo, via intrathecal injection of AAV9::CAG-Acyl-GEGqI virus, revealed that GEGqI expression accelerated the recovery from severe burn injury-induced pain and suppressed hyperalgesic priming in a mouse model of chronic pain. These findings demonstrate that genetically encoded Gq inhibitors have high potential as therapeutics to treat sustained and chronic pain.

Disclosures: A. Dabbs: None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.09/BB7

Topic: E.01. Somatosensation – Pain and Itch

Title: Functionalization of Sodium Alginate Hydrogels for Targeted Use on Nociceptive Pathways in Drosophila

Authors: *N. MCDONALD[1], R. GUERRIERO[2];
[2]Interdisciplinary Program of Neurosci., [1]George Mason Univ., Fairfax, VA

Abstract: Chronic pain management relies heavily on opioid therapeutics, which carry a severe risk of addiction and overdose. To develop safer, non-addictive treatments, we need to explore novel methods of blocking nociceptive pathways, such as localized physical intervention. This project investigates a target-specific biomimetic tissue scaffold designed to physically stop pain signaling through precise mechanical compression at the cellular level. While sodium alginate is an ideal biocompatible polymer for neural engineering, achieving the exact cell and receptor specific anchoring necessary to apply localized mechanical forces in living tissue remains a critical challenge.
We developed a bioconjugation protocol to transform liquid sodium alginate matrix into a targeted structural wrap. Specifically, Class IV nociceptive neurons as they are specialized in nociception in the larval pain response, and they exclusively express the extracellular Pickpocket (ppk1) receptors needed to anchor our antibody-sodium alginate scaffold. Using α-FLAG antibodies, ppk1-FLAG then can be the base of the hydrogel scaffolding. The functionalized mixture was optimized for 2nL microinjections into decoronated Drosophila eggs. The functionalized hydrogel is designed for low-waste microinjection directly into a decoronated egg. Once injected, the immobilized Clone M2 antibodies form a dense, localized capturing mesh that binds specifically to extracellular FLAG-tagged Pickpocket (ppk1) channel complexes on Class

IV sensory neurons. This localized structure uses predictable polymer swelling dynamics to exert controlled mechanical compression on the axon, allowing for localized blocking of nociception. Behavioral nociception was measured in 3rd instar larva after being injected with the matrix; assays included heat nociception and chemical pain using noxious hydrogen peroxide. Neuronal functioning was also measured using electrophysiology on Class IV neurons. Impact of injections on other behavior was measured using DAM2 monitors for activity/sleep, as well as lifespan assays. This strategy introduces a novel methodology by using local structural compression rather than chemical receptor binding to inhibit nociception. By establishing a reliable in vivo model for physical pain attenuation, this research supports the development of targeted, device-like biomaterial therapies. Ultimately, providing precise mechanical alternatives to systemic medications represent a crucial milestone in the clinical effort to eliminate opioid dependency and lower addiction rates.

Disclosures: N. Mcdonald: None. **R. Guerriero:** A. Employment/Salary (full or part-time):; George Mason University.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.10/BB8

Topic: E.01. Somatosensation – Pain and Itch

Title: TEMPERATURE-DEPENDENT PHARMACOLOGICAL MODULATION OF TRPV3 AND TRPM8 CHANNELS CHARACTERIZED BY HIGH-THROUGHPUT AUTOMATED PATCH CLAMP ELECTROPHYSIOLOGY

Authors: *D. R. P. SAUTER[1], B. BADONE[2], P. SCADUTO[5], P. VAELLI[3], G. MOODY[4], A. BARA[2];
[1]Sophion Biosci. A/S, Bedford, MA; [2]Sophion Biosci., Ballerup, Denmark; [3]Neurobio., [4]Sophion Biosci., Bedford, MA; [5]Sophion Biosci. Inc., Bedford, MA

Abstract: Transient receptor potential (TRP) channels are non-selective cation channels critical to thermosensation, nociception, and neuronal signaling. TRPV3 and TRPM8 are thermo-TRP channels implicated in pain pathways, making them important targets for analgesic drug discovery. This study characterized the temperature-dependent pharmacological profiles of TRPV3 and TRPM8 using automated patch clamp (APC) electrophysiology in HEK293 cells stably expressing each channel.
TRPV3 was activated by 2-aminoethoxydiphenyl borate (2-APB) in a concentration-dependent manner at 25°C and 34°C. EC50 values were similar across temperatures (46.05 μM at 25°C; 43.03 μM at 34°C; n=10/group). The activated current was blocked by ruthenium red (RR), with greater potency at 34°C (IC50: 5.3 μM) than 25°C (IC50: 10.7 μM). A concentration-order effect was observed: higher initial RR concentrations produced stronger inhibition (IC50: 2.1 μM vs. 10.7 μM at 25°C).

TRPM8 was activated by racemic menthol (RM) at both 27°C and 18°C, with greater potency at the lower temperature (logEC50: −4.3 at 27°C vs. −4.8 at 18°C). Icilin similarly activated TRPM8 with pronounced temperature dependence (logEC50: −6.7 at 27°C vs. −7.44 at 18°C). Capsazepine inhibited RM-activated TRPM8 in a concentration-dependent manner, with minimal temperature sensitivity (logIC50: −5.3 at 27°C vs. −5.1 at 18°C). Results were reproducible across independent recording platforms (n≥10 per condition).
These findings confirm that TRPV3 and TRPM8 exhibit distinct temperature-dependent pharmacological profiles. TRPM8 agonist sensitivity is strongly enhanced at lower temperatures, while TRPV3 antagonist potency is modestly temperature-dependent. These data provide a reproducible pharmacological characterization framework applicable to TRP channel drug discovery efforts.

Disclosures: D.R.P. Sauter: A. Employment/Salary (full or part-time):; Sophion Bioscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sophion Bioscience. **B. Badone:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **P. Scaduto:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **P. Vaelli:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **G. Moody:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **A. Bara:** A. Employment/Salary (full or part-time):; Sophion Bioscience.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.11/BB9

Topic: E.01. Somatosensation – Pain and Itch

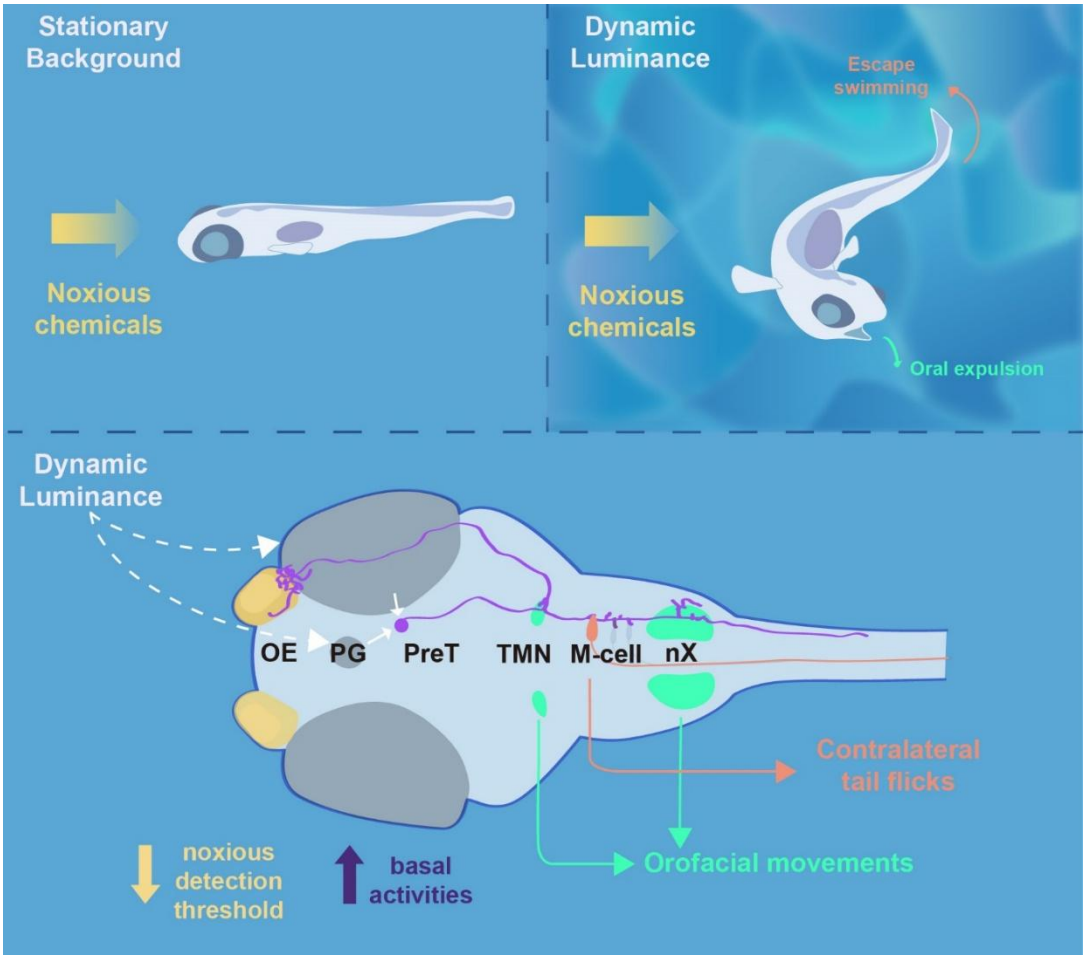
Support: CEBSIT
ShanghaiTech University

Title: A luminance-modulated midbrain nociceptor mediates nocifensive behaviors by coordinating head- and trunk-motor modules

Authors: *Y. YANG;
Ctr. for Excellence in Brain Sci. and Intelligence Technol. (Institute of Neuroscience), Shanghai, China

Abstract: Nociceptors in vertebrates are located in the periphery and respond to localized hazardous stimuli, while the nocifensive responsiveness is largely shaped by circuit-level gain control. Here, we identified a novel kind of midbrain-resident nociceptors that mediates perinasal noxious chemical-induced nocifensive behaviors, which can be enhanced by ambient luminance. These nociceptors are characterized by Pretectum-locating soma, Olfactory Epithelium-innervating peripheral axons, and multiple-collateralizing central axons, termed POEM. POEM directly detects external noxious chemicals and initiates coordinated nocifensive behaviors

manifested as concurrent oral expulsion and tail-driven escape swimming, through simultaneously activating head- and trunk-motor modules. Furthermore, POEM integrates dynamic ambient luminance signals from both retina and pineal gland, enhancing its subthreshold noxious detection and promoting nocifensive behaviors. Our findings reveal a central-resident nociceptor capable of cross-modal integration at the sensory input stage, demonstrating that nociceptors can directly translate non-noxious environmental contexts into flexible nociceptive sensitivity in physiological conditions.



Disclosures: Y. Yang: None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.12/BB10

Topic: E.01. Somatosensation – Pain and Itch

Support: UNM AIM Center (COBRE P20GM121176)

Title: Characterization of the circular RNA landscape of human dorsal root ganglia reveals a neurotrophin-related circRNA modulated by opioid exposure.

Authors: M. KOCH[1], J. B. DEMETER[2], S. R. ALLES[3], K. N. WESTLUND[4], R. EHSANIAN[4], ***J. DE LA PENA**[5];
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Abstract: Opioids are widely prescribed analgesics, but prolonged use produces tolerance and opioid-induced hyperalgesia (OIH). Nociceptors within the dorsal root ganglion (DRG) contribute to both the analgesic and maladaptive effects of opioids. Circular RNAs (circRNAs) are highly stable class of RNA molecules that are enriched in the nervous system. However, the circRNA landscape of the human DRG (hDRG) and its response to opioids remain uncharacterized. In the present study, we characterized the hDRG circRNA landscape and tested whether opioid exposure alters circRNA expression. hDRGs was obtained from ethically consented organ donors. Total RNA sequencing was performed on opioid-exposed donors (toxicology-positive) and age- and sex-matched opioid-negative controls (n=3/group; 2 male, 1 female per group; ages 22-55). circRNAs were quantified with CIRI2/CIRIquant and linear transcripts with HISAT2/StringTie. We identified 20,034 unique circRNAs detected across hDRG, with the most abundant including CDR1as and circHIPK3. Opioid exposure was associated with a global reduction in circRNA abundance (Kolmogorov-Smirnov, $P = 0.019$) and 43 differentially expressed circRNAs (25 up, 18 down; $|\log2FC| \geq 1$, $P \leq 0.005$). Parallel analysis revealed 349 differentially expressed linear transcripts, including neuronal-signaling and immune-related genes. Integrative competitive endogenous RNA network analysis (ceRNA) and RBP motif enrichment (Transite) implicated miRNA- and RBP-mediated regulation. Among opioid-associated circRNAs, circNTRK2, derived from exons 3-6 of NTRK2 (TrkB receptor; BDNF signaling), was downregulated in opioid-exposed hDRG. In an independent in vitro model, repeat morphine exposure of sensory neuron-like cells reduced circNTRK2 expression (one-way ANOVA, $q < 0.05$; technical triplicate), consistent with the hDRG result. We confirmed circNTRK2 identity by RNase R resistance, circular-junction-spanning PCR, and Sanger sequencing (99% identity), and validated nociceptor expression by BaseScope in situ hybridization colocalized with peripherin and TRPV1. These finding establishes the first comprehensive hDRG circRNA landscape, demonstrates opioid-associated circRNA dysregulation, and identifies circNTRK2 as an opioid-modulated, nociceptor-expressed circRNA. Limitations include small sample size and the associative nature of network predictions. These findings nominate circRNAs as a novel post-transcriptional regulatory layer in human nociceptors and a potential substrate for non-opioid analgesic strategies.

Disclosures: M. Koch: None. **J.B. Demeter:** None. **S.R. Alles:** None. **K.N. Westlund:** None. **R. Ehsanian:** None. **J. De La Pena:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.13/BB11

Topic: E.01. Somatosensation – Pain and Itch

Support: CSU LSAMP
CSU SPA
NIH SC2 GM095428-0181

Title: The effects of capsaicin and heat on central sensitization in Manduca sexta: an analysis of TRPA1 channels for involvement in this process

Authors: *A. HAMILTON[1], M. FUSE[2];
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Abstract: Thermal injury is a common cause of chronic pain, as high intensity noxious heat often causes sensitization to pain. Manduca sexta is becoming a model organism for studying sensitization to pain, but there has been relatively little study in how thermal and chemical stimuli specifically induce sensitization. Vertebrates and invertebrates both sense thermal stimuli through a variety of TRP receptors. Many chemical ligands, like capsaicin, also work through these channels, simulating thermal nociception in absence of noxious temperatures. M. sexta may prove a valuable model for testing this thermal and chemical sensitization as it possesses TRPA channels to sense heat similarly to Drosophila melanogaster, but from our phylogenetics it seems to lack the TRPV1 channels that capsaicin usually acts through. We tested the degree of sensitization through ingested, injected, and topically applied capsaicin, as well as testing it alongside two TRP channel inhibitors: capsazepine for TRPV1 and HC-030031 for TRPA1. We found that capsazepine only inhibited capsaicin at exceedingly high doses, where off-target effects were likely, while HC-030031 inhibited capsaicin at 1/10th of the dose when compared to capsazepine. We also tested noxious heat via an 800mW laser to compare the degree of sensitization to that of capsaicin and other previous studies, and we found that the degree of sensitization from all of these sources, (pinch, capsaicin, laser, and cold) was highly similar. Our studies suggest that capsaicin acts via TRPA1 channels, inducing sensitization, potentially on multi-modal nociceptors responsive to thermal stimuli as well.

Disclosures: A. Hamilton: None. **M. Fuse:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.14/BB12

Topic: E.01. Somatosensation – Pain and Itch

Title: Molecular and electrophysiological characterization of cutaneous Schwann cells

Authors: *M. MOOG[1], P. ERNFORS[2];
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Abstract: Sensory Schwann cells in the skin ensheathe free nociceptive nerve endings and directly excite them to convey noxious mechanical stimuli, however, the ion channels expressed in these cells and their roles in nociception remains unexplored. In the present study, we isolated primary cutaneous Schwann cells expressing Tomato using the Sox10 promoter from hind paw mouse skin, maintained them in culture for 2-6 days, and used patch-clamp recordings to record macroscopic ionic currents. Mechanical stimulation (1 to 7 micron displacement) of isolated cells evoked inward currents when voltage was clamped at negative values. In current-clamp experiments, cells typically exhibited resting membrane potentials around -45 to -55 mV and mechanical stimulation evoked 20-30 mV depolarizations. Mechanosensitive currents in sensory Schwann cells exhibited inactivating and non-inactivating components in response to 200 ms displacement, with the inactivating component decaying in 10-20 ms, notably slower than reported for Piezo2 channels. We also observed robust voltage-activated outward currents in nociceptive Schwann cells, arising from voltage-activated potassium (Kv) channels in the Kv1 family, as confirmed single cell RNA Seq and suppression of outward currents by the Kv1 inhibitor, α-Dendrotoxin. In a minority of cells, we measured voltage-activated currents carried by calcium ions. We are currently using genetic, pharmacological and biophysical approaches to define the molecular identity of mechanosensitive and voltage-activated ion channels expressed in nociceptive Schwann cells so their roles in sensing mechanical pain can be further explored.

Disclosures: M. Moog: None. **P. Ernfors:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.15/BB13

Topic: E.01. Somatosensation – Pain and Itch

Support: ZIACL090034-09
ZIACL090035-08
ZIACL090033-09

Title: The Charcot-Marie Tooth 2C Gene Transient Receptor Potential Vanilloid 4 (TRPV4) is Primarily Expressed in Endothelial Cells, but not Neurons in Humans.

Authors: M. G. DUNKELBERG[1], *M. R. SAPIO[2], E. LI[5], S. SHAH[3], C. SABORIO[6], D. MARIC[7], A. GHETTI[8], M. L. WEISS[9], G. LAUMET[10], M. J. IADAROLA[4], A. J. MANNES[5];
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Tallahassee, FL; [4]Perioperative Med., NIH Clin. Ctr., Washington, DC; [5]NIH, Bethesda, MD; [6]Bioengineering, Moffitt Cancer Ctr., Temple Terrace, FL; [7]NINDS/NIH, Bethesda, MD; [8]AnaBios, San Diego, CA; [9]Kansas State Univ. Col. of Vet. Med., Manhattan, KS; [10]Physiol., Michigan State Univ., East Lansing, MI

Abstract: Charcot-Marie-Tooth (CMT) neuropathies are broadly categorized into demyelinating (type 1) and axonal (type 2) neuropathies, usually impacting Schwann cells or peripheral neurons. However, several neuropathy mutations have complex effects on other cells and organ systems converging on the neuropathy phenotype in indirect ways that could point to new neuropathy mechanisms. Gain-of-function mutations in the N-terminal cytoplasmic domain of TRPV4 cause CMT2C. These channelopathy mutations result in increased calcium currents in the TRPV4 channel. While previous studies have shown that ectopic overexpression of the mutant channel in neurons leads to calcium-induced cell death, the mechanism of neuropathy in humans remains debated due to several outstanding questions. TRPV4 has generally been suggested as a sensory transducing channel with restricted neuronal subtype expression, but these gain-of-function mutations appear to cause widespread sensorimotor neuropathy without the paroxysmal pain typically associated with hyperactivation of sensory neurons. We have previously developed a high-fidelity human tissue staining protocol. Using transcriptomics and in situ hybridization, we aimed to characterize the precise cellular expression in human tissues to address the mechanism of TRPV4 hyperactivation in CMT2C. Surprisingly, we found limited evidence of this channel's expression in neurons or Schwann cells in healthy organ donors suggesting it is unlikely that aberrantly activated TRPV4 currents can directly kill neurons. Indeed, we found little evidence of expression of this gene outside of human dermis or various epithelial cell types. Together with a recent proposal that endothelial cell Trpv4 overexpression causes CMT2C-like symptoms in genetic mouse models, we suggest that the involvement of TRPV4 activating mutations may engage an unknown secreted factor or signaling pathway that connects epithelial functions to CMT pathophysiology.

Disclosures: M.G. Dunkelberg: None. **M.R. Sapio:** None. **E. Li:** None. **S. Shah:** None. **C. Saborio:** None. **D. Maric:** None. **A. Ghetti:** A. Employment/Salary (full or part-time):; AnaBios Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AnaBios Corporation. **M.L. Weiss:** None. **G. Laumet:** None. **M.J. Iadarola:** None. **A.J. Mannes:** None.

Poster

PSTR270: Nociceptors, Thermoreceptors, and Pruriceptors

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR270.16/BB14

Topic: F.09. Motor Neurons and Muscle

Title: Integrated In Vitro Strategy for Accelerated Discovery of Sodium Channel Modulators for pain

Authors: *X. GUO;
Innovative CRO Explorer -lCE Biosci. inc, South San Francisco, CA

Abstract: We present an integrated in vitro assay platform for accelerating the evaluation of Nav1.8 sodium channel inhibitors. Using manual patch-clamp on HEK293 cells expressing human Nav1.8, we established robust primary assays for potency and selectivity. The lead compound (VX-548) blocked hNav1.8 with an IC50 of around 0.3 nM and exhibited highly selectivity against other Nav isoforms (Inhibition is less than 20% at 10μM). Across species, the different potency of this compound were observed in native dorsal root ganglion (DRG) neurons: in dissociated DRGs from mouse, rat, monkey, IC50 values of TTX-resistant sodium currents were 300 nM (mouse), 200 nM (rat), and 0.1nM (cynomolgus monkey) on Nav1.8, indicating species shifts. Action potential firing in nociceptive neurons from mouse, rat and cynomolgus monkey was also dose-dependently suppressed, demonstrating functional target engagement. Parallel safety pharmacology screening on a broad panel of ion channels and receptors showed no significant off-target activity: for example, cardiac Nav1.5 and hERG currents were inhibited by <10% at 10 μM, suggesting a >1000-fold safety margin. T By integrating these orthogonal assays under uniform SOPs and analytics, the platform compresses hit-to-lead cycle time signicaicantly delivers directly comparable potency metrics across species and preparations, and provides a de-risking funnel that has already supported IND entry for Nav1.8 (and also other ion channel targets) programs. This cohesive, service-oriented pipeline offers a practical blueprint for bridging preclinical electrophysiology to clinical translation in pain therapeutics.

Disclosures: X. Guo: None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.01/BB15

Topic: E.01. Somatosensation – Pain and Itch

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP24K12313
Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP21K09282

Title: Mesenchymal Stem Cells Reverse Injury Specific Nociceptive Circuit Remodeling Following Peripheral Nerve and Spinal Cord Injury

Authors: *R. FUKUSHI[1], M. SASAKI[2], A. M. TAN[3], S. G. WAXMAN[4], J. D. KOCSIS[5], O. HONMOU[6];
[1]Sapporo Med. Univ. Sch. of Med., Sapporo, Japan; [2]Div. of Neuroscience, Dept. of Physiol., Sapporo Med. Univ., Sapporo, Japan; [3]Neurol., Yale University/VA Connecticut Healthcare Syst., West Haven, CT; [4]Yale Univ. Sch. of Med., New Haven, CT; [5]Neurol., Yale Univ. Sch. of

Medicine, Dept. of Neurol., Cheshire, CT; [6]Neural regenerative medicine, Sapporo Med. Univ. Sch. Med., Sapporo, Japan

Abstract: Introduction Neuropathic pain after peripheral nerve injury (PNI) or spinal cord injury (SCI) remains a major therapeutic challenge. Emerging evidence suggests that distinct nociceptive pathways are recruited depending on the site of injury. Dendritic spines are highly plastic postsynaptic structures that undergo remodeling from thin to mature mushroom shaped spines in response to nociceptive stimulation. We investigated whether PNI and SCI induce distinct patterns of dendritic spine remodeling in pain related central nervous system regions and whether intravenous MSC infusion reverses these abnormalities. **Materials and Methods** Rats underwent spared nerve injury (PNI) or thoracic contusive SCI and received intravenous infusion of MSCs or vehicle (Fresh DMEM) 3 days later. Sham groups undergoing skin incision alone were included in each model for comparison. Pain behaviors were assessed using von Frey and radiant heat tests. At 28 days, Golgi Cox staining was performed in the primary somatosensory cortex (SI), thalamus, and spinal dorsal horn, followed by three dimensional spine and Sholl analyses. AMPA receptor associated gene expression was evaluated by real time PCR. **Results** Both PNI and SCI produced persistent neuropathic pain, whereas infused MSCs significantly improved behavioral outcomes. Distinct injury specific patterns of dendritic spine remodeling were observed. PNI increased mushroom shaped spine density in the superficial dorsal horn (lamina II), SI, and ventral posterior thalamic complex. In contrast, SCI increased mushroom shaped spine density in the deep dorsal horn (lamina V) and thalamic intralaminar nuclei. Sholl analyses demonstrated increased clustering of mushroom shaped spines near neuronal somata within affected regions. Increased expression of AMPA receptor associated genes was observed in the SI after PNI and in the thalamus after SCI, corresponding anatomically to the regions exhibiting dendritic spine dysgenesis. Intravenous infusion of MSCs significantly reduced both injury induced spine remodeling and region specific AMPA gene upregulation. **Conclusions** PNI and SCI induce distinct patterns of structural and molecular alterations within nociceptive regions of the brain and spinal cord. Despite these distinct pathological patterns, intravenous infusion of MSCs suppressed both dendritic spine abnormalities and AMPA related molecular changes while alleviating neuropathic pain. These findings suggest that infused MSCs modulate pain related central nervous system circuits in both PNI and SCI models and support dendritic spine remodeling as a potential morphological signature of neuropathic pain.

Disclosures: R. Fukushi: None. **M. Sasaki:** None. **A.M. Tan:** None. **S.G. Waxman:** None. **J.D. Kocsis:** None. **O. Honmou:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.02/BB16

Topic: E.01. Somatosensation – Pain and Itch

Support: Kenneth Rainin Foundation

Title: Brain network signatures of ulcerative colitis

Authors: ***F. MANDINO**, Z. H. GURSKY, T. KANG, D. J. JUN, E. FAVUZZI, E. M. LAKE; Yale Univ., New Haven, CT

Abstract: Ulcerative colitis is a chronic disorder with no cure that is increasingly recognized to involve not only the gastrointestinal system but also the brain. Yet, the large-scale neural dynamics underlying disease progression remain poorly understood. Here, we investigated brain-wide functional connectivity changes during colitis using a mouse model of dextran sulfate sodium (DSS)-induced inflammation. Adult mice (n=7) underwent longitudinal resting-state functional magnetic resonance imaging (fMRI) during two DSS challenges spaced one-month apart (**Figure 1A**). Connectivity matrices (166×166 regions) were computed to quantify inter-regional blood-oxygen-level dependent (BOLD) signal (a)synchrony changes using linear mixed effect modeling. These analyses revealed reproducible and time-dependent reorganization of functional networks during both DSS exposures, relative to baseline (**Figure 1B**). Specifically, colitis was characterized by enhanced functional coupling within prefrontal regions, including anterior cingulate, implicated in affective evaluation of visceral pain and decision-making, as well as within insular-somatosensory and motor areas, associated with embodied pain processing and awareness. Additional alterations emerged across limbic and brainstem networks during later stages, accompanied by region-specific shifts in network degree. Excitingly, these network-signatures overlap with patterns reported in patients with colitis who have undergone BOLD-fMRI. Together, these findings are a first demonstration that gut inflammation drives structured, time-dependent remodeling of large-scale brain networks in an established mouse model using a clinically accessible imaging modality (BOLD-fMRI).

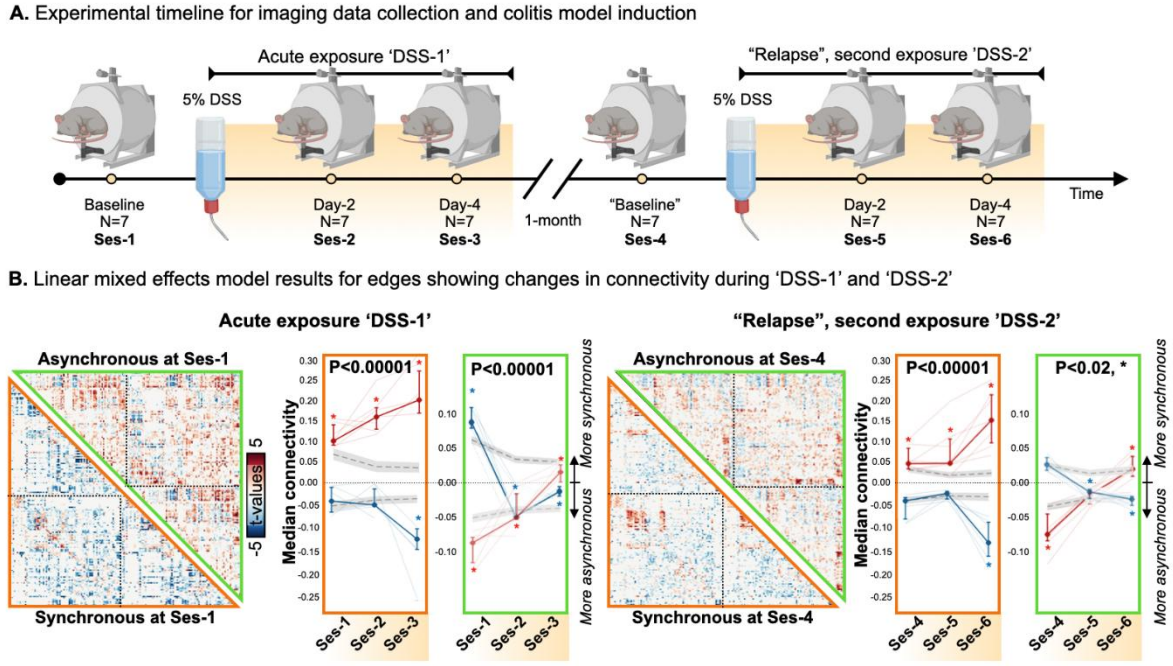


Figure 1. Experimental design and main findings of longitudinal fMRI on DSS-induced colitis. A. Experimental design. Mice underwent resting-state fMRI across baseline and multiple timepoints during dextran sulfate sodium (DSS)-induced colitis. Imaging was performed at baseline (**Ses-1**), during acute inflammation (Day 2–4; **Ses-2–3**), and repeated following recovery with a second DSS challenge one month later (**Ses-4–6**), prior to organ harvest. **B.** Longitudinal alterations in whole-brain functional connectivity. Linear mixed-effects modeling identified connectivity edges showing significant changes across imaging sessions during both the initial (DSS-1) and repeated, "relapse" (DSS-2) inflammatory challenges. Connectivity matrices illustrate representative patterns of network reorganization, with distinct subsets of connections exhibiting increased synchrony (orange) or increased asynchrony (green) relative to baseline. Insets show the temporal evolution of median connectivity strength for significant edge groups across imaging sessions.

Disclosures: F. Mandino: None. **Z.H. Gursky:** None. **T. Kang:** None. **D.J. Jun:** None. **E. Favuzzi:** None. **E.M. Lake:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.03/BB17

Topic: E.01. Somatosensation – Pain and Itch

Title: Opioid-escalated chronic postsurgical pai: role of DNA methylation in developing brain pain circuitry

Authors: *Q. LI;
Anesthesiol., Johns Hopkins Univ. and Univ. of Maryland, Baltimore, MD

Abstract: Chronic postsurgical pain (CPSP) is a clinical problem that affects surgical patients, including pediatric patients. Although opioids are commonly used to relieve pain after surgery, evidence suggests that opioids may increase the risk of persistent pain. DNA methylation has emerged as critical regulators of neural development and pain processing, yet their role in opioid-induced alterations of developing brain pain circuitry remains poorly understood. P18 mice underwent left spared nerve injury (SNI) to establish a model of CPSP. After surgery, mice received 5mg/kg morphine (MPH) for 3 wks. Subsequently, animals were treated with the 0.5mg/kg DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine (DAC) for another 3 wks. Weekly von Frey test and Hargreaves test at 3 wk and 6 wk were conducted to assess mechanical and thermal hypersensitivity. Anterior cingulate cortex (ACC) and insular cortex (IC) were harvested. IHC, WB and qPCR were performed to test cellular or molecular alterations in these regions. To translate this study to patients, we applied a human iPSC-derived brain organoid (hBO), which is a 3D culture platform that models key structural and cellular features, to test how MPH alters neuronal activity in human brain. 5μM was applied in hBO at week 8-11 and cell viability, Ca2+ imaging, and IHC for c-fos were performed to examinate neuronal activity in hBOs. Our results indicate MPH relieves pain in first week after SNI but elevates pain response since wk 2. Consistent application of MPH reduces the μ-opioid receptors in ACC and IC. In addition, MPH upregulates neuronal activity, excitatory synapses, and mTOR pathway. Increased DNA methylation enzymes, such as 5-mC and DNMT1, is involved in these alterations. Administration of DAC reduces susceptibility to chronic pain and reverse cellular and molecular alterations in these regions. In hBO study, MPH increases cell viability, Ca2+ transient peak amplitude, and c-fos, which indicates consistent application of opioid activates selected neurons in human brain tissue. Conclusion. Chronic opioid exposure following surgery contributes to persistent pain by consuming opioid receptors through DNA methylation mechanisms. Inhibition of DNA methylation with DAC alleviates established pain hypersensitivity, supporting a critical role for epigenetic regulation in opioid-escalated CPSP. Targeting DNA methylation pathways may represent a novel therapeutic strategy for preventing or treating chronic pain in patients receiving prolonged opioid therapy.

Disclosures: Q. Li: None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.04/BB18

Topic: E.01. Somatosensation – Pain and Itch

Support: R01NS143697-01
R35HL177406-01
R01NS134647-01A1

Title: Inhibition of histone demethylase LSD1 alleviates opioid addiction and opioid-induced hyperalgesia

Authors: Y. HE[1], *Z. J. WANG[2];
[1]Midwestern Univ., Downes Grove, IL; [2]UIC, Chicago, IL

Abstract: As an essential chromatin modifier, lysine-specific demethylase 1 (LSD1) functions as a transcriptional coregulator by modulating histone methylation. Its participation in opioid use disorder remains unexplored. This study aimed to investigate whether LSD1 mediates epigenetic maladaptation induced by chronic opioid. Mice were treated with morphine by intracerebroventricular (*i.c.v.*) injections. We found repeated brain administrations of sub-analgesic dose of morphine (2 nmol/day, *i.c.v.*, 5 days) elicited opioid tolerance and dependence in mice as determined by the tail-flick assay and naloxone-precipitated jumping test, respectively. Meanwhile, we observed the presence of evoked hypersensitivity to mechanical and thermal stimuli in chronic morphine treated mice by the von Frey filaments assessment and Hargreaves radiation heat test, respectively. Therefore, antinociceptive addiction and opioid-induced hyperalgesia (OIH) co-occurred in mice after chronic central exposure of morphine. In this mouse model of opioid addiction and hyperalgesia, treatment with RN-1 (3 nmol/day, *i.c.v.,* 3 days), a selective irreversible inhibitor of LSD1, significantly attenuated opioid antinociceptive tolerance and physical dependence. In addition, RN-1 treatment effectively reduced mechanical allodynia and heat hyperalgesia, indicating substantial alleviation of OIH. To complement pharmacological inhibition, we further targeted LSD1 by siRNA knockdown. LSD1 siRNA (3 nmol/day, *i.c.v.*, 3 days) dramatically reduced both addiction and hyperalgesia induced by chronic morphine. These results demonstrated for the first time that LSD1 serves as a key epigenetic regulator of opioid addiction and hyperalgesia. Our findings reveal the functional participation of LSD1 in the development of analgesic tolerance, physical dependence, and OIH, which highlighted the possibility of a new intervention target to treat these adverse conditions associated with chronic opioid use.

Disclosures: Y. He: None. **Z.J. Wang:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.05/BB19

Topic: E.01. Somatosensation – Pain and Itch

Support: Weill Neurohub Postdoctoral Fellowship
NIH NINDS R01 (1R01NS136739)
Marcus Precision Medicine Transformative Integrated Research Award

Title: Directional Limbic-Thalamic Connectivity Supports Subjective Pain Perception and Analgesia from Deep Brain Stimulation

Authors: *R. VATSYAYAN[1], E. F. CHANG[3], S. V. SARMA[4], P. SHIRVALKAR[2];
[1]Neurolog. Surgery, [2]Neurolog. Surgery and Anesthesiol., Univ. of California San Francisco, San Francisco, CA; [3]Univ. of California, San Francisco, Piedmont, CA; [4]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: Chronic pain is increasingly recognized as a brain network disorder rather than dysfunction of a single region. Although deep brain stimulation (DBS) can alleviate chronic pain, the neural mechanisms underlying pain perception and therapeutic relief remain poorly understood. We hypothesized that top-down limbic circuits encode ongoing pain severity and that DBS modifies these networks to produce analgesia.**Methods/Materials:** Eight patients with chronic neuropathic pain implanted with intracranial stereo-EEG electrodes underwent repeated brain circuit mapping during naturally fluctuating pain states. Single-pulse electrical stimulation was delivered across pain-relevant regions including the mid-cingulate cortex, insula, thalamus, and periventricular gray. Stimulation-evoked potentials were quantified using measures of effective connectivity, including response amplitude, RMS power, explained variance, engagement, and phase-based synchronization. Dynamical systems modeling characterized stimulus-response relationships and inter-regional delays. We used machine learning to evaluate whether pain state could be discriminated from stimulation-evoked network responses and examined spontaneous connectivity to characterize underlying network dynamics.**Results:** Pain state could be discriminated above chance using stimulation-evoked responses, indicating that directional limbic connectivity contains information related to ongoing pain. The strongest effects involved cingulate, insular, and thalamic circuits. Pain-related modulation was evident across multiple response features. Linear state-space modeling identified changes in response dynamics and inter-regional interactions associated with pain severity in a subset of patients. Descending limbic pathways generally outperformed ascending sensory pathways and other networks in pain-state discrimination. Therapeutic brain stimulation altered pain-sensitive network features, whereas ineffective stimulation produced weaker or inconsistent effects. Pain-related network features exhibited both common trends across patients and inter-individual variability.**Conclusions:** These findings suggest that chronic pain is encoded within a distributed limbic network whose connectivity dynamically tracks pain state and is selectively modified by therapeutic stimulation. Stimulation-evoked connectivity may serve as a causal

biomarker of ongoing pain, supporting a network-based model of DBS analgesia and the development of biomarker-guided adaptive neuromodulation strategies.

Disclosures: R. Vatsyayan: None. **E.F. Chang:** None. **S.V. Sarma:** None. **P. Shirvalkar:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.06/BB20

Topic: E.01. Somatosensation – Pain and Itch

Support: FAPESP 2024/01917-0
FAPESP 2022/04387-6

Title: Sex-Specific Amygdala Activation in Persistent Pain

Authors: *A. BRAGA DIAS[1], N. UREL-CARNEIRO[2], C. TAMAI[2], D. B. SOUZA[2]; [1]Sao Paulo State University/ Sch. of Pharmaceut. Sci. - Araraquara, Araraquara, Brazil; [2]Sao Paulo State University/ Sch. of Pharmaceut. Sci., Araraquara, Brazil

Abstract: Chronic pain is a global health issue with a higher prevalence in women. As the amygdaloid complex is key for its affective component, this study aimed to evaluate sex differences in central (CeA) and basolateral (BLA) amygdala activation using a hyperalgesic priming model in mice. To investigate this, male and female Swiss Webster mice (60 days old) were assigned to either control or hyperalgesic priming groups (n=7-8/group). The priming protocol consisted of a plantar incision followed by a local injection of prostaglandin E2 (PGE2) to induce persistent hypersensitivity. Nociceptive responses were assessed using the Von Frey test and the Mouse Grimace Scale (MGS). Subsequently, brain tissues were processed for immunofluorescence to evaluate CeA and BLA activation via DeltaFosB expression. Behavioral assessments confirmed persistent pain development. The Von Frey test repeated measures ANOVA revealed significant mechanical hyperalgesia compared to baseline in both sexes ($F_{(5,25)} = 20.68$, $p < 0.05$). However, the MGS revealed a sex difference, while both groups showed increased pain expressions over time ($F_{(5,25)} = 12.90$, $p < 0.05$), males exhibited significantly higher facial pain scores than females ($F_{(5,25)} = 6.86$, $p < 0.05$). Interestingly, these behavioral differences corresponded to distinct neural activation patterns. In the CeA, the repeated measures ANOVA revealed only a main effect of condition ($F_{(1, 27)} = 14.71$, $p < 0.001$), demonstrating that animals with pain exhibit higher neural activation regardless of sex. In the BLA, the analysis revealed a significant sex and condition interaction ($F_{(1, 29)} = 4.64$, $p = 0.040$). Tukey's HSD post-hoc test confirmed that hyperalgesic priming significantly increased BLA activation only in males ($p = 0.006$), with no significant change in females. Our findings highlight a sexually dimorphic response in the amygdala during persistent pain. While both sexes develop mechanical hypersensitivity and engage the CeA similarly, the male-specific activation of the

BLA directly correlates with their higher facial pain expression. This indicates that males and females utilize fundamentally different affective processing mechanisms during hyperalgesia.

Disclosures: A. Braga Dias: None. **N. Urel-Carneiro:** None. **C. Tamai:** None. **D.B. Souza:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.07/BB21

Topic: E.01. Somatosensation – Pain and Itch

Support: U01EY034709
2T32GM132006-06

Title: Chronic Dry Eye Increases Recruitment of Brain Regions Implicated in Affective Pain and Stress in Mouse

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Abstract: Chronic dry eye disease is often characterized by persistent intractable ocular pain, and individuals with dry-eye disease show higher prevalence of anxiety and depression, implicating plasticity in underlying central processing. Despite its clinical prevalence, the central neural pathways of corneal pain and changes accompanying its chronification remain incompletely characterized. We used FosTRAP2 activity-dependent genetic cell labeling and whole brain light sheet imaging to map and characterize activation across the mouse brain in a chronic dry eye model (lacrimal gland excision; LGE) and in intact controls, under baseline, corneal stimulus evoked, and handling-stress conditions. Using both a hypothesis directed framework applied to atlas-registered region-level cell counts and an exploratory cluster enhancement analysis at the voxel level, we identified networks activated during acute corneal stimulation in intact and LGE mice, providing a systems level map of central corneal pain processing. Several regions previously associated with corneal pain showed an increased number of FosTRAP-labeled neurons in LGE mice in response to corneal hypertonic saline application compared to intact mice (e.g. lateral parabrachial nucleus, nucleus raphe magnus). In some of these regions, handling-stress alone induced a greater number of FosTRAPed neurons in LGE mice (e.g. posterior thalamus, zona incerta, anterior cingulate cortex). Exploratory voxel cluster analysis additionally revealed LGE-induced changes in FosTRAP-labeled clusters within regions associated with pain and stress such as locus coeruleus and paraventricular hypothalamus. Activation data was integrated with the Allen Institute mouse brain transcriptomic and connectivity atlases to characterize the molecular identity and circuit relations of activated populations. Our results suggest that chronic dry-eye heightens stimulus-evoked responses in

central corneal pain pathways, and recruits affective and stress modulating circuits consistent with anxiety and depression-like behaviors observed in chronic dry-eye.

Disclosures: S.S. Reynolds: None. **K. Niyonkuru:** None. **W. Renthal:** None. **I.D. Meng:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.08/BB22

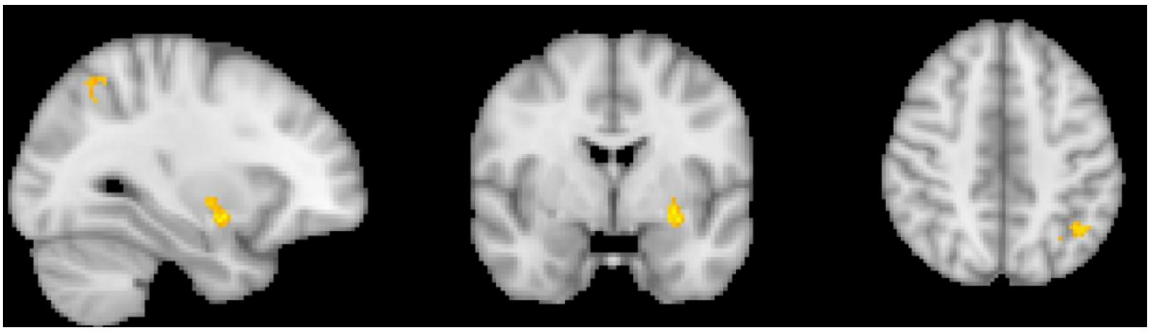
Topic: E.01. Somatosensation – Pain and Itch

Support: Psychiatry Department, University of Rochester Medical Center.

Title: Brain response to pleasant touch in chronic pain patients

Authors: C. ABBOUD[1], J. NADDOUR[2], I. PERINI[3], ***P. Y. GEHA**[1];
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Abstract: Introduction: Chronic pain is characterized by anhedonia, a feature increasingly recognized as contributing to the elevated risk of comorbidities such as substance use disorder. Despite its importance, anhedonia in chronic pain remains poorly understood. Here, we used psychophysical testing and functional magnetic resonance imaging (fMRI) to investigate pleasant touch processing in chronic low-back pain (CLBP).Methods: Sixteen CLBP patients and 15 age- and sex-matched healthy controls (HC) participated. CLBP patients reported pain for at least 1 year at ≥4/10 intensity. Study procedures were completed over 2 visits. During Visit 1, participants underwent a psychophysical task in which the ventral surface of the left forearm was brushed at two velocities: slow (3 cm/s) and fast (9 cm/s). Slow stroking preferentially activates C-tactile afferents and is perceived as pleasant. Participants rated stimulus intensity and liking using the generalized labeled magnitude scale and labeled hedonic scale, respectively. During Visit 2, participants underwent fMRI while receiving the same tactile stimulation. Imaging data were preprocessed using FSL. Brain responses were assessed using the general linear model implemented in FSL-FEAT. Results: Groups did not differ in perceived intensity of either slow or fast touch. Contrary to our hypothesis, CLBP patients reported significantly greater liking of touch than HC (slow: HC 5.87 ± 1.77, CLBP 14.56 ± 2.36; fast: HC 3.83 ± 2.12, CLBP 7.70 ± 2.81; $p = 0.008$). All analyses controlled for age, sex, and body mass index. fMRI revealed no group differences during fast touch. In contrast, slow touch elicited significant group differences in the left putamen, amygdala, and posterior parietal cortex ($p < 0.05$, whole-brain corrected) (Figure 1).Conclusions: Increased liking of pleasant touch in CLBP may reflect distraction from ongoing pain. Altered responses in limbic and striatal regions suggest disrupted affective processing of pleasant sensory stimuli, with reduced neural responses despite enhanced subjective liking.



HC exhibit increased response to slow touch in the left amygdala, putamen, and posterior parietal cortex compared to CLBP patients ($p < 0.05$, whole brain corrected)

Disclosures: C. Abboud: None. **J. Naddour:** None. **I. Perini:** None. **P.Y. Geha:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.09/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Title: Central and peripheral mechanisms of pain in fibromyalgia: scoping review

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Abstract: Introduction: Fibromyalgia is characterized by widespread musculoskeletal pain, frequently accompanied by fatigue, depression, anxiety, sleep disturbances, and cognitive impairment. It is the second most prevalent rheumatic disease. Diagnosis remains challenging due to symptom overlap with conditions such as carpal tunnel syndrome, Raynaud's syndrome, and Sjögren's syndrome. Neuropathic pain and autonomic dysfunction suggest involvement of the nervous system. Ion channels, neurotransmitters, and neuromodulators are thought to contribute to its pathophysiology. Additionally, small fiber neuropathy (SFN) has been identified as a potential contributor to chronic widespread pain. Methods: A literature review was conducted using Web of Science, MEDLINE, Scopus, EBSCOhost, Ovid, and Google Scholar. The search strategy was based on Medical Subject Headings (MeSH) terms and related keywords. Preclinical studies, clinical studies, and experimental models describing imaging, neurophysiological, anatomical, structural, neurochemical, or immunological characteristics of the central and peripheral nervous systems associated with pain in fibromyalgia were included. Studies without standardized pain measures, those published in languages other than English or Spanish without adequate translation, and those lacking full-text access were excluded. A narrative synthesis was performed. Results: Title/abstract screening for the initial searches has been completed (5,163 studies after duplicate removal), 2654 studies were selected for inclusion at this stage. The full-text screening phase for this set of studies has been initiated. Literature searches were updated on May 28, 2026, to incorporate the most recent studies. Ongoing activities: Duplicates identified in the updated searches are currently being removed, after which title/abstract screening will be conducted for the studies resulting from this phase. Full-text screening of studies identified in the initial searches is ongoing. Preliminary results highlights neurochemical, immunological, and structural alterations in both central and peripheral nervous systems contributing to pain sensation in fibromyalgia. Conclusions: An integrative perspective supports the interaction between central sensitization and peripheral mechanisms, including small fiber pathology. This approach may improve diagnostic accuracy and guide targeted therapeutic strategies.

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Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

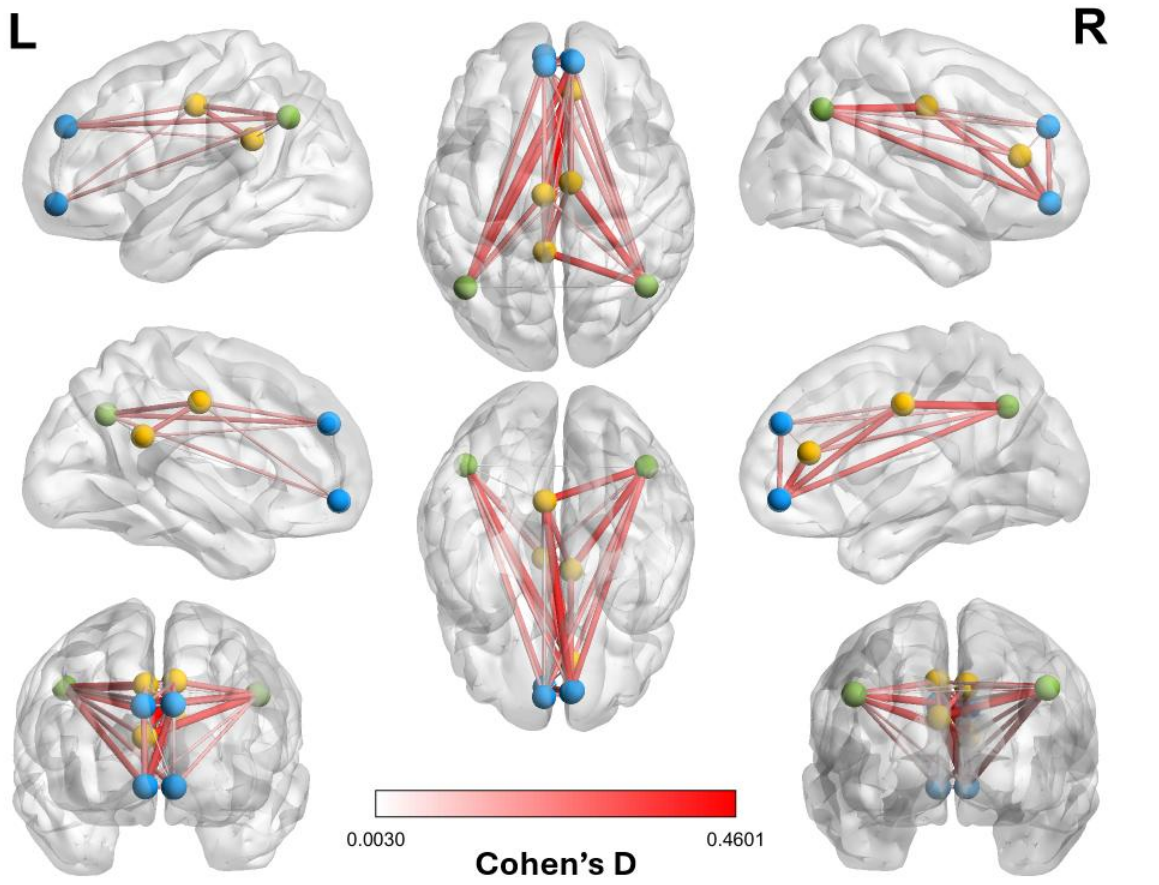
Program #/Poster #: PSTR271.10/BB23

Topic: E.01. Somatosensation – Pain and Itch

Title: Alterations in the functional brain network connectivity of women with interstitial cystitis bladder pain syndrome

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Abstract: Interstitial Cystitis/bladder pain syndrome (IC/BPS) affects 3.3-7.9 million women in the United States and is often accompanied by both urinary frequency and urgency. Approximately 75% of women with IC/BPS also report additional painful areas beyond the pelvis. Women with IC/BPS and widespread pain beyond the pelvis often experience central sensitization. Understanding the centrally-driven mechanisms of chronic pelvic pain prior to the onset of neuropathic pain is instrumental for neuromodulation. This preliminary study aims to identify associated brain networks in women with IC/BPS and widespread pain. Functional and structural magnetic resonance imaging (MRI) from women with IC/BPS and widespread pain (n=96), defined as >3 non-pelvic regions, and healthy female controls (n=33) from the MAPP-II study underwent standard preprocessing in the CONN toolbox. Participants voided and then ingested ~350 mL of water prior to functional MRI scanning. Resting-state functional brain networks were created from the Automatic Anatomical Labelling (AAL) atlas. ROI-to-ROI connectivity was assessed with a multivariate parametric general linear model (GLM) with ROI-level inferences. Network-based inferences were performed with the Network-Based Statistics toolbox. ROI-specific analyses suggest that women with IC/BPS and widespread pain exhibit weaker connectivity from the bilateral mid-cingulate cortices versus the healthy female controls (Left MCC: $F(4,310)=5.73$, p-FDR=0.016518; Right MCC: $F(4,310)=4.77$, p-FDR=0.042929). NBS identified one sub-network exhibiting the same pattern of functional connectivity (Mass=317.20, p-FDR = 0.036384). Bilateral hypoconnectivity of the mid-cingulate cortices to the medial orbitofrontal and superior frontal cortices and angular gyrus were identified, corresponding to the default mode and salient networks. The results of this study suggest that women with IC/BPS and widespread pain present with a reduced cortical response to the visceral bladder sensation and highlight the mid-cingulate cortex as a key area for future study.



Disclosures: M. Houston: None. **Y. Zhang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); HillMed Inc.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.12/BB24

Topic: E.01. Somatosensation – Pain and Itch

Support: CIHR Project Grant PJT-17525
CIHR Foundation Grant 246515
Edwards PhD Fellowship in Chronic Pain Research from the Louise and Alan Edwards Foundation

Title: Mapping KOR-Dependent Opioid Relapse Mechanisms in Chronic Pain Using a Novel Low-Cost, High-Throughput Tissue Clearing Platform

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Abstract: Background: Chronic pain affects approximately 22% of the population and is frequently managed with long-term opioid therapy despite risks of misuse, dependence, and opioid use disorder (OUD). Buprenorphine hydrochloride is an effective treatment for OUD and acts as a kappa opioid receptor (KOR) antagonist, a system implicated in stress, negative affect, and relapse vulnerability. However, the circuit mechanisms underlying KOR-dependent effects in opioid withdrawal and relapse remain poorly understood. Whole-brain tissue clearing and volumetric imaging enable unbiased circuit discovery but are limited by cost and throughput.Methods: Equal numbers of male and female C57BL/6J mice underwent spared nerve injury (SNI) or sham surgery to model chronic neuropathic pain. Animals then acquired oral morphine self-administration and were assessed for relapse-like behavior following complete abstinence, buprenorphine-, or morphine-assisted gradual dose reduction (withdrawal) and reinstatement. To test KOR involvement, behavioral outcomes were compared between wild-type and KOR−/− mice. In parallel, we developed a low-cost, 3D-printed electrophoretic tissue clearing platform capable of processing up to 24 whole mouse brains simultaneously for large-scale immunohistochemistry and light-sheet imaging.Results: Buprenorphine intervention reduced relapse-like responding following morphine self-administration in wild-type mice. This effect was absent in KOR−/− mice, supporting a KOR-dependent mechanism of action. We further validated a high-throughput tissue clearing platform with a total material cost under $750 USD, enabling scalable whole-brain processing while maintaining compatibility with volumetric immunolabeling and imaging pipelines.Conclusions: These findings provide behavioral evidence that KOR signaling contributes to buprenorphine-mediated reduction of opioid relapse-like behaviours and introduce an accessible platform for high-throughput whole-brain imaging. By reducing cost and increasing throughput, this system enables larger cohort studies and more comprehensive circuit-level analyses.Future Directions: We will combine conditioned cue re-exposure paradigms with whole-brain c-Fos mapping to identify neural ensembles engaged during cue-induced opioid craving. Integrating relapse-related behavioral phenotyping with unbiased activity screening in wild-type and KOR−/− mice will prioritize KOR-sensitive regions for downstream multiplex fluorescence in situ hybridization (FISH) and cell-type-specific molecular profiling.

Disclosures: H. Derue: None. **A. Ribeiro-da-Silva:** None. **J.S. Mogil:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

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Program #/Poster #: PSTR271.13/BB25

Topic: E.01. Somatosensation – Pain and Itch

Support: NRF Grant RS-2024-00335546
NRF Grant RS-2024-00402116
NRF Grant RS-2022-NR070151

Title: Prefrontal-Limbic Oscillatory Dynamics and Connectivity in Rat Models of Chronic Pain with Affective Comorbidities

Authors: *H. CHAI[1], H. JEONG[1], **Y. LEE**[2], T. KIM[4], C. KOH[4], S. MIN[4], H. JUNG[4], S. JUN[1,2,3];
[1]Dept. of Electronic and Electrical Engin., [2]Ewha Brain Inst., [3]Div. of Brain & Cognitive Sci., Ewha Womans Univ., Seoul, Korea, Republic of; [4]Dept. of Neurosurg., Yonsei Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: Chronic neuropathic pain is frequently accompanied by affective disturbances. However, how these alterations evolve during pain progression and influence neural circuitry remains unclear. Clinically, these emotional comorbidities, such as depression and anxiety, severely exacerbate pain perception and functional disability, often leading to significantly reduced responsiveness to conventional neuromodulation therapies and less durable outcomes. In this study, we investigated the circuit-level pathophysiological mechanisms underlying chronic pain by utilizing *in vivo* multichannel electrophysiological recordings across the prefrontal-limbic network, focusing on the medial prefrontal cortex (mPFC), nucleus accumbens (NAc), and basolateral amygdala (BLA). To model the clinical features of treatment-resistant chronic pain accompanied by affective dysfunction, we compared four experimental groups: control, spared nerve injury (SNI), olfactory bulbectomy (OB_X) and a combined SNI+OB_X model. By integrating the robust nociceptive features of the SNI model with the distinct emotional dysregulation of the OB_X model, we successfully established a comprehensive experimental framework that closely recapitulates the multi-dimensional, complex clinical phenotype of treatment-resistant chronic pain. Local field potential (LFP) analyses revealed prominent, model-dependent alterations in oscillatory activity across specific frequency bands. Furthermore, functional connectivity within the network was quantified using the phase-locking value (PLV) to assess interregional phase synchronization. These electrophysiological findings demonstrate that chronic pain with comorbid affective dysfunction severely disrupts neural synchronization and functional connectivity within the mPFC-NAc-BLA circuit. Such changes likely reflect maladaptive reorganization that compromises critical prefrontal-limbic coordination

Disclosures: H. Chai: None. **H. Jeong:** None. **Y. Lee:** None. **T. Kim:** None. **C. Koh:** None. **S. Min:** None. **H. Jung:** None. **S. Jun:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.14/BB26

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant UG3NS137282
NIH training grant T32GM075770

Title: Investigating cortical correlates of phantom limb pain after lower limb amputation

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Abstract: Phantom limb pain (PLP) affects most individuals with amputation and can lead to reduced activity and quality of life. The underlying neural mechanisms of PLP are not well understood, and there is ongoing controversy about the degree of cortical remapping that occurs after amputation and its association with PLP. Furthermore, nearly all research on PLP neural mechanisms has focused on upper limb amputation. The purpose of this study is to better understand differences in brain activity associated with lower limb amputation and PLP. We used functional magnetic resonance imaging (fMRI) to examine differences in cortical activation in individuals with lower limb amputation with and without PLP as compared to control participants without amputation. fMRI measured cortical activity while participants followed visual cues and attempted movements of ankle (i.e., dorsiflexion/plantarflexion) and toe (i.e., flexion/extension). Participants also observed tactile stimulation of the plantar surface of the left and right foot with a blunt object and imagined the sensation. Motor runs (four conditions) and sensory runs (two conditions) followed a block randomized design. Data processing included cortical surface reconstruction, motion and distortion correction, and brain extraction. For each run, a general linear model was fit with four regressors for motor runs and two regressors for sensory runs. fMRI scans have been completed for six participants with amputation (n=5 with PLP, n=1 without PLP) and five able-bodied participants. In examining preliminary results from three participants (one with PLP, one without PLP, one able-bodied), using a z-statistic threshold of 3.4, the participant with PLP shows an increased volume of sensorimotor cortex activation. This increased area of activation was observed during actual and attempted movements of both intact and amputated sides and during imagined touch. There was also evidence of bilateral activation of medial sensorimotor cortex (i.e., regions of M1 and S1 associated with foot/leg) in the individuals with amputation, while activity was constrained to the contralateral hemisphere in the able-bodied participant. Continued data collection with a planned sample size of 10 per group (n=30 total) will build upon these results. Increasing our understanding of the cortical mechanisms of PLP after lower limb amputation can inform PLP treatment strategies.

Disclosures: K.J. Falbo: None. **M. Duran:** None. **K. Ding:** None. **E. Pirondini:** None. **J.L. Collinger:** None. **L.E. Fisher:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.15/BB27

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant UG3NS137282

Title: Cortical modulation of sensorimotor rhythms following lower limb amputation

Authors: *K. DING[1], M. DURAN[1], K. J. FALBO[2], B. COFFMAN[3], J. L. COLLINGER[4], L. E. FISHER[4];
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Abstract: Over 70% of people living with lower-limb amputation (LLA) experience phantom limb pain (PLP), which significantly affects quality of life and prosthesis use. Neuroimaging studies have mostly focused on upper limb amputation cases and have reported mixed results in terms of cortical representation and sensorimotor activity in relation to PLP. Here, we explore these relationships in individuals with LLA using magnetoencephalogram (MEG), which provides higher temporal resolution than fMRI to characterize cortical sensorimotor responses. Understanding the cortical representation of the lower limb in PLP will inform future treatment development of PLP. In this study, we recorded MEG from participants with unilateral LLA with and without PLP, as well as participants with intact limbs. MEG sessions contained both motor and sensory blocks. In the motor blocks, participants performed cued ankle plantar/dorsiflexion or toe flexion/extension to match the movements seen on a first-person video. In the sensory blocks, participants viewed videos of a foot being touched with a reflex percussion hammer and imagined the sensation. Participants performed these tasks with their left and right leg, with 50 trials for each task. MEG data were collected on a 306-channel MEGIN Neuromag TRIUX (Helsinki, Finland) system at 1000 Hz using standard MEG recording procedures. Data was preprocessed by removing bad channels and applying temporal signal-space separation with a 4-second buffer. Sensor level event-related desynchronization (ERD) of the mu (8-13Hz) and beta (13-30Hz) bands were computed. A total of 76 gradiometer sensors covering the sensorimotor cortex were used in this preliminary analysis. For each task condition, ERD was averaged across channels within each hemisphere and across all trials. Peak average ERD within 0-2 seconds relative to the task cue was obtained. Preliminary results from 10 participants (4 intact limb, 6 LLA) showed ERD in the mu and beta bands following ankle or toe movements. We observed bilateral desynchronization, though contralateral ERD was stronger. For participants with LLA, peak average ERD in the beta band during attempted ankle movement on the amputated side was decreased compared to that with the intact side. Ongoing data collection and further analysis at the source level will provide more information about peak activity, as well as latency and area of modulation. These results will inform whether cortical modulation of sensorimotor rhythm differs between participants with and without PLP.

Disclosures: K. Ding: None. **M. Duran:** None. **K.J. Falbo:** None. **B. Coffman:** None. **J.L. Collinger:** None. **L.E. Fisher:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

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Program #/Poster #: PSTR271.16/BB28

Topic: E.01. Somatosensation – Pain and Itch

Title: Curcumin-derived bioactive compounds modulate lipid and amino acid metabolism-related gene expression in the amygdala of male neuropathic rats

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Abstract: We previously reported that curcumin-derived bioactive compounds alter lipid- and amino acid-related metabolites in amygdala of animals with neuropathic pain (NP), suggesting supraspinal metabolic remodeling of curcumin in NP. Because the amygdala regulates affective pain, we examined related metabolic gene expression in the amygdala of male SNL rats treated with curcumin C3 Complex® (CUR) or bisdemethoxycurcumin (BDMC). Male rats were randomized into Sham + V, SNL + V, SNL + 100CUR (100 mg/kg BW CUR), or SNL + 50BDMC (50mg/kg BW BDMC) groups (n=6/group). Four weeks after Sham or SNL surgery, rats received CUR, BDMC, or corn oil vehicle (V) for six weeks. Amygdala tissue was analyzed by RT-qPCR for genes related to amino acid and lipid metabolism pathways. Data were analyzed by one-way ANOVA with Fisher's LSD test. SNL broadly altered metabolic pathway-related transcripts. For GABA regulation and substrate transport, SNL rats showed increased Gad1, Slc6a1, and Slc2a1 compared to Sham rats, while CUR and BDMC decreased Gad1 and Slc6a1 relative to vehicle. For tryptophan-kynurenine/NAD+ metabolism, SNL rats showed increased Ido1, Kmo, and Qprt compared to Sham rats; CUR decreased all three, while BDMC decreaased Ido1 and Qprt compared to vehicle. For fatty acid and phospholipid pathways, SNL rats showed increased Acsl3, Chka, and Pla2g4a compared to Sham rats; CUR decreased Pla2g4a but had little effect on Ppara and Acsl6 relative to vehicle. For sphingolipid metabolism, SNL rats showed increased Smpd1 and limited changes of Cers2 and Asah1 compared to Sham rats. For arginine/nitric oxide and polyamine metabolism, SNL rats showed increased Arg1, Arg2, Nos1, Nos2, and Odc1 compared to Sham rats; CUR decreased Nos1 and BDMC decreased Arg1 and Nos2 relative to vehicle. For plasmalogen/ether lipid pathways, SNL rats showed decreased Agps and increased Pla2g15 compared to Sham rats; CUR decreased Pla2g15 while BDMC decreased Far1 relative to vehicle. For lipid transport/regulation, SNL rats showed decreased Nr1h3 and increased Abca1 compared to Sham rats; both CUR and BDMC decreased Abca1 and CUR also increased Nfe2l2 relative to vehicle, while Apoe showed limited effects. In conclusion, CUR and BDMC partially normalized SNL-induced distinct pathway components under NP conditions, especially genes related to GABA regulation, kynurenine/NAD+ metabolism, phospholipid remodeling, arginine/nitric oxide signaling, plasmalogen-associated lipid processing, and lipid efflux. These results suggest that the amino acid and lipid metabolism-related pathways may contribute to the beneficial effects of curcumin-derived bioactive compounds in NP.

Disclosures: X. Liu: None. **G. Ji:** None. **T. Kiritoshi:** None. **V. Neugebauer:** None. **C. Shen:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.17/BB29

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
NIH grant R01NS118731
NIH grant R01NS120395
NIH grant R01NS129552

Title: Amygdala endocannabinoid and astrocyte signaling contributes to mGlu5 modulation of neuropathic pain

Authors: *V. NEUGEBAUER, M. MAZZITELLI, N. ANTENUCCI, K. LEONARD;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Metabotropic glutamate receptor 5 (mGlu5) in the amygdala plays an important role in pain-related synaptic plasticity and behavioral modulation, but actions may be subregion-specific and interactions with endogenous cannabinoid and glial signaling in the amygdala circuits represent an important knowledge gap. We found previously that systemic application of alloswitch-1, a photoswitchable negative allosteric modulator of mGlu5, produced inhibitory effects on neuropathic pain behavior through thalamic and cortical mechanisms, but mGlu5 blockade in the basolateral amygdala (BLA) produced unexpected pro-nociceptive effects whereas previous data had shown that mGlu5 blockade in the CeA was antinociceptive. Here, we tested the hypothesis that mGlu5 blockade alters endocannabinoid signaling in the amygdala and that astrocyte-dependent mechanisms contribute to mGlu5 modulation of pain-related behavior of adult rats in the spared nerve injury (SNI) model. LC-MS/MS analysis of endocannabinoid-related lipid mediators showed that systemic alloswitch-1 decreased the levels of anandamide (AEA), but not 2-arachidonoylglycerol (2-AG), selectively in the central amygdala (CeA) but not BLA, suggesting that mGlu5 inhibition may interfere with potentially beneficial CeA AEA signaling in neuropathic pain. Next we explored the behavioral significance of this interaction and found that intra-CeA alloswitch-1 increased mechanical withdrawal thresholds and decreased vocalizations, consistent with an anti-nociceptive effect of CeA mGlu5 blockade in neuropathic pain. A fatty acid amide hydrolase (FAAH) inhibitor (URB597) alone did not significantly alter pain-related behaviors, but co-administration of URB597 with alloswitch-1 decreased or prevented the anti-nociceptive effects of alloswitch-1 on evoked behaviors. The combination also had anxiolytic effects. An astrocyte metabolic inhibitor (fluorocitrate, FCA) further enhanced pain-like behaviors, whereas co-administration of FCA with alloswitch-1 partially reversed these effects, suggesting that the anti-nociceptive actions of CeA mGlu5 blockade can not simply explained by astrocyte inhibition. These findings suggest that mGlu5 inhibition in the CeA decreases neuropathic pain-related behavior and that this effect is modulated by AEA signaling and potentially by astrocyte-dependent mechanisms. Together, these data support a functional interaction among mGlu5, endocannabinoid signaling, and glial

mechanisms in the amygdala and identify CeA mGlu5-dependent signaling as a potential regulator of pain-related amygdala output in neuropathic pain.

Disclosures: V. Neugebauer: None. **M. Mazzitelli:** None. **N. Antenucci:** None. **K. Leonard:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.18/BB30

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grants NS038261
NS106902
NS109255

Title: Interleukin-17a signaling modulates neuroimmune activation in the central amygdala and contributes to chronic neuropathic pain

Authors: *G. JI, T. KIRITOSHI, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuroimmune activation in the brain has been implicated in various CNS functions and disorders. The interleukin-17 (IL-17) proinflammatory cytokine family plays a central role in various CNS diseases. Recent evidence suggests that IL-17 acting on its specific receptor (IL-17R) expressed by immune, glial, and neuronal cells, is implicated in peripheral and spinal pain mechanisms, but its potential effects on pain modulation in the brain are largely unexplored. Our previous studies demonstrated that the amygdala with its central nucleus (CeA) is an important brain center involved in pain modulation. In this study, we investigated the amygdala neuroimmune activation and the role of IL-17a and its receptor IL-17Ra in pain modulation in the CeA in the spinal nerve ligation (SNL) mouse model of chronic neuropathic pain. We found that markers for microglia (IBA1) and astrocytes (GFAP) expression significantly increased in left and right CeA in SNL mice 1 and 4 weeks post-induction. Co-labeling with neuronal marker (NeuN) showed that IL-17Ra is expressed on neurons and astrocytes, but not on microglia cells in the CeA. Up-regulation of IL-17Ra expression was detected in both neurons and astrocytes in the CeA in SNL mice. Stereotaxic injection of IL-17a protein into the CeA decreased mechanical thresholds and light box explorations in normal mice, suggesting that IL-17a in the CeA induces hypersensitivity and anxiogenic behaviors. Application of IL-17Ra neutralizing antibody into the CeA increased mechanical thresholds and light box explorations in SNL mice, suggesting that blockade of IL-17Ra decreases sensory and affective pain behaviors. Upregulation of IL-17Ra on astrocytes and neurons in the CeA in SNL and behavioral effects of IL-17a and IL-17Ra modulation suggest that IL-17a signaling in the CeA plays an important role in the neuroimmune signaling in pain conditions and contributes to the development of chronic neuropathic pain.

Disclosures: G. Ji: None. **T. Kiritoshi:** None. **V. Neugebauer:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

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Program #/Poster #: PSTR271.19/BB31

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
NIH grant R01NS129552

Title: Sex-dependent effects of chemogenetic manipulations of central amygdala microglia in neuropathic pain

Authors: *N. ANTENUCCI, C. ARAGON CARDONELL, O. PONOMAREVA, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuroimmune signaling in the amygdala contributes to the sensory and affective dimensions of chronic pain, but the causal role of central amygdala (CeA) microglia remains incompletely understood. Microglia are responsive to injury-induced plasticity and may modulate pain-related circuit function in a sex-dependent manner. Initial viral-promoter validation studies in rats (unpublished data) revealed that CD68 promoter-driven AAV expression was not microglia-selective in the CeA, but instead labeled non-microglial cells, including CRF-expressing neurons. This prompted us to adopt a Cx3cr1-Cre/AAV-DIO strategy for the selective chemogenetic manipulation of microglia. Cx3cr1-Cre mice received unilateral right CeA injections of Cre-dependent excitatory Gq-DREADD, inhibitory Gi-DREADD, or empty control virus. To test whether microglial activation is sufficient to alter behavior, naïve mice received CeA Gq-DREADD or control virus. To test whether microglial inhibition attenuates neuropathic pain, mice received CeA Gi-DREADD or control virus followed three days later by spinal nerve ligation (SNL). Mechanical withdrawal thresholds were measured longitudinally using von Frey testing. Three weeks after SNL or equivalent time points in naïve mice, animals received systemic CNO for seven days, followed by behavioral testing. SNL mechanical withdrawal thresholds decreased after nerve injury, consistent with the development of neuropathic mechanical hypersensitivity. Repeated chemogenetic inhibition of CeA microglia with Gi-DREADD increased mechanical withdrawal thresholds after CNO treatment in both males and females, suggesting decreased neuropathic hypersensitivity. In males, SNL induced anxiety-like avoidance behaviors in the open field test (OFT) and in the light-dark box (LDB), whereas Gi-DREADD activation of CeA microglia decreased avoidance behaviors in both tests. In naïve males, Gq-DREADD activation of CeA microglia induced anxiety-like avoidance behaviors in the OFT and LDB. In females, behavioral effects were more complex and appeared to differ from males, with Gq activation and Gi inhibition producing distinct patterns in both tests. These findings suggest that CeA microglia can causally modulate pain-related

hypersensitivity and affective behaviors. Inhibition of CeA microglia decreased hypersensitivity in males and females but anxiety-like behaviors only in males. Activation of CeA microglia in naïve animals tended to promote avoidance-like behavioral changes, particularly in males. The data suggest that CeA microglia contribute to chronic pain-related circuit dysfunction in a sex-dependent manner.

Disclosures: N. Antenucci: None. **C. Aragon Cardonell:** None. **O. Ponomareva:** None. **V. Neugebauer:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.20/BB32

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant NS038261

Title: Facilitatory effects of amygdala P2Y14 receptor activation on pain-like behaviors.

Authors: *M. MAZZITELLI[1], N. ANTENUCCI[1], D. SALVEMINI[2], V. NEUGEBAUER[1]; [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]St. Louis Univ. Dept. of Pharmacol. and Physiological Sci., Saint Louis, MO

Abstract: Pain is a multidimensional experience with a significant averse-affective component. Because of its complexity, pain remains an important medical challenge. The amygdala, a key limbic brain structure, plays a critical role in the emotional-affective dimensions of behavior and in pain modulation. Within the amygdala, the central nucleus (CeA) serves as a major output center, and neuroplastic changes in the CeA have been mechanistically linked to pain-related behaviors across various pain conditions. Therefore, interventions aimed at reducing maladaptive amygdala plasticity may offer promising therapeutic strategies for pain management. P2Y purinergic receptors are G-protein coupled receptors that have emerged as potential therapeutic targets in different models of chronic pain. Specifically, P2Y14 receptor (P2Y14R) is a Gi-protein coupled receptor expressed in glial cells and neurons, and has pro-inflammatory and pro-nociceptive functions during pain development and maintenance. P2Y14R has several endogenous ligands, but uridine diphosphate(UDP)-glucose was identified to be the most potent agonist. In this study, we assessed the effects of the pharmacological activation of P2Y14R using UDP-glucose on pain-like behaviors under normal conditions.Selective PY214R activation in the CeA was achieved by the stereotaxic application of UDP-glucose. Emotional responses (evoked vocalizations), mechanical withdrawal thresholds (electronic von Frey and paw pressure test), and spontaneous (grimace score) behaviors were used to measure the effects of intra-CeA UDP-glucose in adult naïve rats. Selective P2Y14R activation resulted in facilitatory effects on evoked vocalizations, mechanical withdrawal responses, and grimace score under normal conditions.These data suggest that activation of P2Y14R in the amygdala drives pain-related

behaviors and provide evidence to support a potential role of P2Y14R in the development and maintenance of pain.

Disclosures: M. Mazzitelli: None. **N. Antenucci:** None. **D. Salvemini:** None. **V. Neugebauer:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.21/CC1

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
NIH grant R01NS118731
NIH grant R01NS120395

Title: Contributions of central amygdala chemokine CXCL10/CXCR3 signaling to pain-related behaviors under normal and neuropathic pain conditions.

Authors: *T. KIRITOSHI, G. JI, V. NEUGEBAUER;
Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The central nucleus of the amygdala (CeA) is a key regulator of pain modulation and its emotional-affective aspects. Emerging evidence suggests the critical involvement of CeA neuroimmune signaling in pain-related behaviors and neuroplastic changes. Our previous transcriptomic analyses identified C-X-C motif chemokine ligand 10 (CXCL10) as a prominently upregulated neuroimmune signaling gene in the CeA under chronic neuropathic pain conditions. However, the contributions of CeA CXCL10 signaling to pain-related behaviors remain to be determined. Here we examined the effects of exogenous CXCL10 and pharmacological blockade of its receptor CXCR3 in the CeA on sensory and anxiety-like behaviors under baseline and chronic neuropathic pain conditions. Four weeks after L5 spinal nerve ligation (SNL neuropathic pain model) or sham surgery, recombinant CXCL10 or a selective CXCR3 antagonist (NBI 74330) was injected into the CeA. Mechanical sensitivity was measured by von Frey test. Anxiety-like behaviors were assessed using light-dark box, open field test, and elevated plus maze. Our data suggest that intra-CeA administration of recombinant CXCL10 increases mechanical sensitivity in sham controls without clear effects on anxiety-like behaviors. NBI 74330 showed a trend to modulate anxiety-like behaviors without clear effects on mechanical sensitivity. These results suggest potential contributions of CeA CXCL10/CXCR3 signaling to pain-related behaviors at the 4-week time point after SNL.

Disclosures: T. Kiritoshi: None. **G. Ji:** None. **V. Neugebauer:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

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Program #/Poster #: PSTR271.22/CC2

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS038261
NIH grant AA027096

Title: Transcriptomic dynamics in the central amygdala during the transition from acute to chronic neuropathic pain.

Authors: *J. D. CARDENAS TORO[1], C. BUSTAMANTE[4], P. D. PRESTO[2], B. R. KISBY[2], G. JI[2], O. PONOMAREVA[3], S. SHANMUGAM[5], V. NEUGEBAUER[2], I. PONOMAREV[2]; [1]Pharmacol. & Neurosciences, [2]Pharmacol. and Neurosci., [3]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [4]Univ. of California Santa Barbara, Santa barbara, CA; [5]Pharmacol. and Neurosci., TTUHSC, Lubbock, TX

Abstract: Chronic neuropathic pain is a complex disorder arising from nervous system damage, yet the mechanisms driving its development and persistence are not well understood. The central nucleus of the amygdala (CeA), a critical hub for the emotional-affective dimension of pain, undergoes neuroplastic changes across pain states. However, cell type-specific molecular mechanisms underlying the transition from acute to chronic pain (chronification of pain) are not well understood. To address this gap in knowledge, we performed single-nucleus RNA sequencing (snRNA-seq) in the CeA at the acute (1 week) and chronic (4 weeks) stages after spinal nerve ligation (SNL), a model of neuropathic pain. After quality control, 25621 cells were clustered using Seurat, and we identified 17 cell types based on canonical cell-type marker expression. Bioinformatics analysis identified differentially expressed genes (DEGs), functional groups, and molecular pathways affected by pain induction at different stages in males and females. The results were largely stage- and sex-specific, suggesting mechanistic differences in chronification of pain in males and females. In males, sensory perception of pain (*Grm1, Grm2, Kcna2*) and response to dopamine (*Htr2a, Gnaq*) were consistently over-represented across stages. In contrast, cellular response to TNF (*Bdnf, Fos, Rora*), macrophage activation (*Cd200, Jun*) , inhibitory postsynaptic potential (*Gabrb3, Grin2a*), and macromolecule methylation (*Prmt1, Mettl1, Mettl2)* were stage-specific. In females, Wnt signaling (*Wnk1, Apoe*) was consistently over-represented across stages, while membrane depolarization (*Grik1, Cacna1a*), interleukin-6 production (*P2rx7, Stat3, Xbp1*), positive regulation of gliogenesis (*Mag, Sox10*), and negative regulation of cytokine production (*Dicer1*) were stage-specific. These results identify cell type-specific molecular profiles potentially underlying chronification of pain in males and females.

Disclosures: J.D. Cardenas Toro: None. **C. Bustamante:** None. **P.D. Presto:** None. **B.R. Kisby:** None. **G. Ji:** None. **O. Ponomareva:** None. **S. Shanmugam:** None. **V. Neugebauer:** None. **I. Ponomarev:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.23/CC3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant U01AA020911
Bowles Center for Alcohol Studies

Title: Dynorphin Signaling in the BNST Modulates Basal Pain Sensitivity in a Sex-Dependent Manner

Authors: *M. CAZA[1], J. A. WOJICK, PhD[2], T. L. KASH[2];
[1]UNC Chapel Hill, Chapel Hill, NC; [2]Pharmacol., The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Alcohol use disorder (AUD) is driven in part by negative reinforcement, where individuals drink to escape aversive withdrawal states including anxiety, dysphoria, and hyperalgesia. The dynorphin/kappa opioid receptor (KOR) system is a key mediator of these aversive states and is well established as a modulator of nociception; KOR is engaged in chronic pain states. The bed nucleus of the stria terminalis (BNST) contains a dense population of dynorphin-expressing neurons and has been implicated in anxiety and alcohol withdrawal. We hypothesized that BNST dynorphin will impact baseline nociceptive thresholds and is necessary for nociceptive hypersensitivity following binge alcohol exposure. To test this, we used AAV8-*hSyn*-GFP-Cre to knockdown dynorphin in the BNST of $Pdyn^{fl/fl}$ mice and compared to controls transfected with AAV8-*hSyn*-GFP. Mice then underwent the drinking in the dark (DID) model of binge-like alcohol drinking for three weeks. Mechanical (Von Frey) and thermal (Hargreaves) nociceptive sensitivity were assessed before and after DID. Additionally, anxiety-like behavior was assessed via novelty-suppressed feeding (NSF) and elevated zero maze (EZM) before drinking, and EZM and open field testing after drinking. Knockdown males exhibited higher mechanical thresholds and longer thermal withdrawal latencies compared to controls. We did not observe differences in females at baseline. Following DID, we did not see the same sex-specific effects in males, suggesting binge-like alcohol exposure may normalize dynorphin-dependent nociceptive sensitivity. These findings reveal a novel sex-specific role for BNST dynorphin in nociception and suggest that alcohol may engage this system to alter nociceptive thresholds in males.

Disclosures: M. Caza: None. **J.A. Wojick:** None. **T.L. Kash:** None.

Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.24/CC4

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R16GM153598
Kahn Family Foundation

Title: Sex-specific alterations of the amygdala and hypothalamus in a rodent model of early life pain.

Authors: C. MICHAUD[1], A. DEL GRECO[1], S. PELLETIER[1], B. WESLER[2], C. NORTON[1], A. GBOLAHAN[3], J. H. GRABER[4], R. A. GRINDLE[5], *M. A. BURMAN[1];
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Abstract: Patients who spend time in the neonatal intensive care unit (NICU) demonstrate increased vulnerability to a variety of later-life psychology and physiological conditions, including chronic pain. Our lab uses rodent model of a NICU-like experience, in which newborn rat pups are subjected to repeated hindpaw needle pricks and brief maternal separation over the first week of life. Our lab has previously observed that rats subjected to this model produces a fear conditioning-induced tactile hypersensitivity that peaks during the juvenile period. Moreover, we find that the early life pain and stress create changes in the size of pain-related cell populations, including Corticotropin Releasing Hormone (*crh*)-, Somatostatin (*sst)*-, and Enkephalin (*penk)*-expressing cells in the Central Nucleus of the Amygdala (CeA) only in male rats. Despite similar behavioral effects, we have yet to identify specific early life pain-related changes in females. This project uses hi-plex *in situ* hybridization (RNA Scope) examines expression of 12 different pain and stress-related makers, as well as markers of key cell types (*oxt, pdyn, crh, gad65, pvalb, nts, slc17a7, avp, prkcd, pomc, sst,* penk) in the Central Nucleus of the Amygdala (CeA), Basolateral Amygdala (BLA), Paraventricular Nucleus of the Hypothalamus (PVN), Anterior Hypothalamus (HA), and Ventromedial Hypothalamus (HVM) in neonatal (postnatal day 12) and juvenile (postnatal day 24) male and female rats with 4-5 subjects per group. Preliminary results confirm that changes in the right CeA are largely limited to males, whereas we see greater changes in the anterior hypothalamus, especially in neurotensin-expressing cells, primarily in females. Additional analyses demonstrate sex and hemispheric differences, as well as differential co-expression of key neuropeptides. The results confirm that early life medical trauma produces lasting sexually dimorphic changes to pain- and stress-relevant brain circuits that impact later function.

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Poster

PSTR271: Brain Circuits and Mechanisms of Pain

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01DA062509
NIH Grant R01DA49924
NIH Grant T32DA007261
NIH Grant L70NS134089

Title: Adaptations in the anteromedial thalamic nucleus and its projections to anterior cingulate cortex in a mouse model of chronic neuropathic pain

Authors: *H. WANG, R. D. GRAHAM, T. HAGE, R. SLIVICKI, R. DESOVA, A. VELEZ, J. P. GOLDEN, M. CREED;
Washington Univ. in St. Louis, St. Louis, MO

Abstract: Chronic pain affects millions of individuals and is notoriously difficult to treat. One of the most debilitating symptoms that patients experience is the ongoing spontaneous pain that occurs in absence of external stimuli. Beyond the sensory component, this pain is perceived as deeply distressing, intrusive, and emotionally exhausting. The anterior cingulate cortex (ACC) is critical for this affective pain processing. Although traditionally considered as a homogenous structure in the pain literature, ACC contains both rostral and dorsal subdivisions with distinct and dissociable roles. Rostral ACC (rACC) has been studied extensively as a modulator of affective pain processing, but how dorsal ACC (dACC), a major clinical neuromodulation target, integrates with the ascending affective pain pathway remains poorly understood. Inputs from the thalamus are crucial for encoding the emotional aspects of nociceptive signals in cortical areas, and thalamocortical neurons are critical for activity-dependent modulation and information processing. Our functional circuit mapping revealed that anteromedial nucleus of the thalamus (AM), a higher order thalamic nucleus, projects widely to ACC and is the exclusive source of thalamic input to dACC. Using patch-clamp electrophysiology, we found that CCI reduces spontaneous synaptic excitation onto dACC neurons. We sought to determine the synaptic mechanism by which chronic neuropathic pain alters the AM-dACC pathway, and the causal contribution of this pathway to spontaneous and affective pain behaviors (SPBs). Given that AM activity is integral to attention, reward, and emotional processing, our overall hypothesis is chronic neuropathic pain weakens the functional AM-dACC connection, and this weakening is causally related to SPBs, without affecting nociception per se. Using the chronic constriction injury (CCI) mouse model of chronic neuropathic pain, we found that CCI mice exhibit SPBs, which includes licking, shaking, or attending the injured limbs, and these behaviors capture the negative affective component of spontaneous pain. Paradoxically, CCI is associated with increased maximum tonic firing rate in dACC-projecting AM neurons, and that tonically activating dACC-projecting AM neurons optogenetically at 20Hz induced a conditioned place aversion. Together, these results suggest that chronic neuropathic pain alters thalamocortical regulation of dACC activity and suggest that disrupting tonic activity of the AM-cingulate pathway may reduce negative affective symptoms of chronic pain.

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Poster

PSTR271: Brain Circuits and Mechanisms of Pain

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR271.26/CC6

Topic: E.01. Somatosensation – Pain and Itch

Support: HHMI

Title: Temporal single-cell profiling of the parabrachial Calca neurons reveals molecular dynamics driving nociplastic pain

Authors: *S. PARK[1], F. CAO[2], R. D. PALMITER[3];
[1]Howard Hughes Med. Inst. and Univ. of Washington, Seattle, WA; [2]Psychology, Western Washington Univ., Bellingham, WA; [3]Univ. of Washington, Seattle, WA

Abstract: Parabrachial *Calca* neurons are necessary for chronic pain and sufficient to drive nociplastic pain, but how they sustain a pain state that outlasts its trigger is unknown. We performed temporal single-cell mRNA sequencing of the parabrachial nucleus (PBN) across the onset, chronic, and recovery phases of *Calca* neuron-driven tactile allodynia, using fixed-tissue profiling and reference-atlas registration to track molecularly defined populations over time. Activation broadly induced immediate-early genes, after which *Calca* neurons displayed changes in expression of genes that affect signaling and synaptic plasticity, with bidirectional changes that mirrored the onset and resolution of allodynia. The gene encoding brain-derived neurotrophic factor (*Bdnf*) remained persistently elevated in the chronic phase. BDNF infusion in the PBN prolonged allodynia, whereas blockade of its receptor (TrkB) shortened it, and inactivating the Bdnf gene in *Calca* neurons abolished their hyperexcitability, attenuated allodynia, and relieved pain in a migraine model. These observations pinpoint BDNF as a driver of persistent nociplastic pain.

Disclosures: S. Park: None. **F. Cao:** None. **R.D. Palmiter:** None.

Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.01/CC7

Topic: E.02. Somatosensation – Touch

Support: R00NS112612
R01NS142032

Title: Circuit Remapping After Unilateral Whisker Denervation

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Abstract: Cortical remapping is defined as reorganization of cortical connections between neighboring regions of primary sensory cortex (S1) territory. Cortical map plasticity can occur after hand amputation, for example lip-responsive activation can be detected in the neighboring deprived S1 hand region. Remapping has been shown to occur after limb loss and denervation injury in both humans and animal models, but the synaptic mechanism underlying this remapping is unknown. We use a mouse model of whisker denervation to characterize these synaptic changes. Denervation of the whiskers is achieved by unilateral transection of the infraorbital nerve (IONX), where many adaptations of neural activity mimic those detected in people after limb loss. After IONX, there is an increase in neural excitability in the deprived (contralateral to whisker denervation injury) primary somatosensory barrel cortex (S1BC). This hyperexcitability is thought to be driven by a potentiated corpus callosum (CC) connection from the intact S1BC. We hypothesize that the intact to deprived S1BC CC connection drives increased deprived S1BC excitability after IONX; this activity recruits invasion of nose-responsive activity after IONX. To test this hypothesis, we will modulate CC activity with chemogenetics and test map plasticity with optogenetics and electrophysiology. In order to establish how S1 maps change after IONX, first we characterized the connection between S1 nose and S1BC in naïve animals. The S1 nose region was optogenetically activated and neural responses in neighboring S1BC were measured with whole cell electrophysiology. The ratio of excitation to inhibition (E/I ratio) was measured, with increased inhibition relative to excitation in naïve animals. We hypothesize that IONX-induced hyperexcitability will shift the E/I ratio to favor excitation, thus allowing cortical remapping to occur. The results of this study will identify the synaptic mechanisms underlying circuitry changes after denervation injury. Understanding these mechanisms will allow for the identification of therapeutic targets to support recovery after limb loss.

Disclosures: M. Eisenfeld: None. **F.S. Nugent:** None. **E. Petrus:** None.

Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.02/CC8

Topic: E.02. Somatosensation – Touch

Support: NIH Grant R00NS112612
NIH Grant R01NS142032

Title: Changes in White Matter Integrity After Unilateral Whisker Denervation

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Abstract: Unilateral limb loss causes changes in brain circuitry, which may impair sensory and motor function. One hallmark of this circuit reorganization is the loss of white matter (WM) integrity within the WM tracts connecting bilateral sensory and motor cortical regions. This degradation likely impairs functional recovery, because these pathways are essential for coordinating accurate sensory perception and motor execution between the intact limb and the residual limb or a prosthesis. In addition to reduced WM integrity, cortical neuron excitability increases in individuals after unilateral limb loss. It is unknown if WM integrity loss is caused by chronic neuronal hyperexcitability after limb loss. To address this question, we have developed a mouse model of denervation injury which replicates both phenotypes. Because mice predominately rely on their whiskers to navigate their environment, we model unilateral sensory loss by unilaterally transecting the infraorbital nerve (IONX), effectively denervating all the whiskers on one side of the face. This model allows us to investigate the mechanisms driving alterations in WM integrity and neural excitability after unilateral injury. Maintaining WM integrity requires healthy neuronal axons and their insulating myelin sheath, which together support proper signal integration. We used immunohistochemistry and electron microscopy to quantify myelin basic protein (MBP) expression and properties of axon myelination respectively in the WM tracts of mice after IONX injury. Our preliminary data suggest that WM integrity is bidirectionally modified over time. Acutely, MBP fluorescence and axon health improve in the WM tracts below the sensory-deprived cortex. However, at a chronic timepoint, MBP fluorescence decreases and axon health degrades after IONX. We hypothesize that these findings are activity-dependent, as highly active neurons recruit myelin from neighboring oligodendrocytes. Because neurons are hyperexcitable after IONX, oligodendrocytes may initially respond by increasing the myelination of their axons. However, a prolonged hyperexcitable circuit may create an unhealthy environment where both neurons and oligodendrocytes undergo programmed cell death. By uncovering the mechanisms underlying WM integrity loss after denervation injury, these findings may identify novel therapeutic targets to preserve WM integrity and enhance recovery in patients with limb loss.

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Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.03/CC9

Topic: E.02. Somatosensation – Touch

Support: R00NS112612
R01NS142032

Title: The Pasta Test: A Behavioral Test to Detect Orofacial Function in a Mouse Model of Trigeminal Nerve Injury

Authors: *N. KOGANTI[1,2], S. COLLIER[1,3], M. CAMPANILE[1,3], L. IYER[1,3], E. PETRUS[1]; [1]Uniformed Services Univ., Bethesda, MD; [2]Univ. of Rochester, Rochester, NY; [3]Henry M. Jackson Fndn. for the Advancement of Military Med., Bethesda, MD

Abstract: Trauma-induced Trigeminal Neuropathic Pain (TNP) is a chronic pain condition that is caused by certain dental procedures, motor vehicle accidents, or military injuries. Despite surgical interventions, 20% of people develop chronic symptoms which impair speaking, chewing, and facial expressions during interpersonal interactions. Central sensitization in TNP is characterized by hypersensitivity to non-painful touch and ectopic pain beyond the territory innervated by the injured trigeminal nerve branch. These functional adaptations are likely due to increased neural activity in the peripheral and central neurons that process sensation. We use an adult mouse model to mimic orofacial pain which is achieved by transecting the infraorbital branch (IONX) of the trigeminal nerve. After IONX, rodents have been reported to experience orofacial pain in adjacent non-injured areas on the face and jaw. In this study, we use a simple orofacial function assay, the pasta biting test, to investigate the effects of IONX on orofacial function in mice. We hypothesize that injury to the infraorbital nerve will impact pasta biting behavior. This may be detected as a significant reduction in feeding efficiency compared to sham-operated controls, and is detected as changes in biting amount and frequency. Our results will determine the effect of IONX on orofacial function in mice, indicating that pain after injury to the infraorbital nerve in mice is analogous to pain phenotypes experienced in humans after trigeminal nerve injury. The long-term goal of our lab is to identify the cortical circuits and molecular mechanisms that cause central sensitization after trigeminal nerve injury.

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Poster

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Program #/Poster #: PSTR272.04/CC10

Topic: E.02. Somatosensation – Touch

Support: R00NS112612
R01NS142032
F31NS143385

Title: Thalamocortical Input Reduction and Microglial Activity in the Somatosensory Cortex after Sensory Loss

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Abstract: Throughout life the brain retains the ability to respond to changes in sensory experience. Injury to sensory systems can lead to sensory loss, triggering reorganization of sensory circuitry. Adaptive reorganization may support recovery by potentiating circuitry dedicated to processing the preserved sensory inputs, while maladaptive plasticity could impair recovery due to aberrant circuit remodeling. However, which parts of the sensory circuit and the mechanisms that drive remodeling after injury-induced sensory loss remain unknown. To determine how sensory circuit reorganization occurs, we utilize a mouse model of unilateral whisker denervation. Excitatory inputs arise from the whiskers, continue through the thalamus, and arrive into specialized, barrel shaped structures in layer 4 (L4) of the primary somatosensory barrel cortex (S1BC). Thalamocortical (TC) inputs from the thalamus to cortex retain capacity for plasticity after sensory deprivation, and this connection is expected to be altered after whisker denervation. Whisker denervation reduces feed forward sensory drive from the thalamus into the deprived somatosensory cortex, generating a new population of underused synapses. Microglia remove synapses in an activity dependent manner, targeting weak and underused synapses while preserving strong and active ones. This removal is known to occur in juvenile systems, but the involvement of microglia in targeted synapse removal in adults is less well studied. We hypothesize that whisker denervation in adult mice leads to a loss of TC innervation along the deprived pathway, which is mediated by microglia. The levels of VGlut2-positive thalamocortical innervation, detected by immunohistochemistry, and the prevalence and morphology of microglia in S1BC were measured after whisker denervation at 7and 28 days(D) after whisker denervation. We identified a sex specific response to whisker denervation in adult mice. At 7D, females show reduced VGlut2 intensity in the deprived S1BC which returns to sham levels at 28D. Males show no significant changes in TC synaptic density at any timepoint. Microglial morphology was time- and sex-dependent. Females showed increased ramified morphology 7D after sensory loss but returned to sham levels at 28D. Males show no change in morphology at any timepoint. This work establishes a sex-dependent relationship between excitatory circuit changes and microglial activity following sensory denervation in adult circuits. A more complete understanding of the mechanisms by which neural circuitry changes after sensory loss may support future interventions to better serve people after injuries that cause sensory loss.

Disclosures: S. Collier: None. **L. Iyer:** None. **K.R. Byrnes:** None. **E. Petrus:** None.

Poster

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Program #/Poster #: PSTR272.05/CC11

Topic: E.02. Somatosensation – Touch

Support: R00NS112612
R01NS142032

Title: Sensory denervation drives persistent neuronal hyperexcitability and white matter remodeling in callosal circuits

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Abstract: Unilateral peripheral nerve injury and limb loss are associated with persistent cortical hyperexcitability and reduced white matter integrity in the corpus callosum, yet the cellular mechanisms linking sensory deprivation to long-term circuit dysfunction remain poorly understood. We use unilateral infraorbital nerve transection (IONX), a mouse model of permanent sensory denervation, to investigate adaptations in activity and white matter integrity of callosally projecting neurons of primary somatosensory barrel cortex (S1BC). We hypothesized that chronic denervation-induced hyperactivity disrupts neuronal and axonal health in interhemispheric circuits. To test this, we examined transcriptional, electrophysiological, and structural adaptations in callosally-projecting neurons at acute (2 week) and chronic (2 month) timepoints following IONX. Callosally-projecting neurons exhibited decreased expression of the voltage-gated potassium channel gene *Kcnq5*, a regulator of neuronal excitability, 2 months after IONX. The myelin-associated gene *Plp1* was also reduced at this chronic timepoint, suggesting progressive alterations in myelin structural integrity. Whole-cell recordings revealed persistent hyperexcitability of callosally projecting layer 5 neurons, characterized by increased action potential firing, depolarized resting membrane potential, and reduced rheobase at both 2 weeks and 2 months after injury. Chronic denervation additionally resulted in reduced action potential amplitude and less dynamic action potential kinetics. Structural analysis demonstrated remodeling of nodes of Ranvier within callosal axons following denervation. Nodal gap length (Nav1.6) was significantly reduced 2 weeks after IONX, while overall paranode-node-paranode length (Caspr-Nav1.6-Caspr) was significantly reduced at chronic timepoints, indicating persistent nodal plasticity that may alter axonal conduction properties. Together, these findings demonstrate that unilateral sensory denervation induces coordinated transcriptional, functional, and structural adaptations in callosal circuits. Persistent hyperexcitability coupled with nodal remodeling may contribute to impaired interhemispheric communication and reduced white matter integrity following sensory loss. These results identify potential targets underlying long-term circuit dysfunction after peripheral nerve injury.

Disclosures: L. Iyer: None. **E. Petrus:** None.

Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR272.06/CC12

Topic: E.02. Somatosensation – Touch

Support: NIH Intramural Research Program, NINDS

Title: Reactivated thalamocortical plasticity alters perceptual learning and memory in adult mice

Authors: *H. JIE[1], N. POTHAYEE[1], Z.-D. DENG[2], A. P. KORETSKY[1];
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Abstract: Adult sensory cortex retains latent plasticity after peripheral input loss, but whether this plasticity improves perception and how behavioral learning interacts with it remain unclear. We investigated this question in adult mice after unilateral infraorbital nerve transection by combining whisker-based perceptual learning, electrophysiology, and pharmacological blockade of GluN2B-containing NMDA receptors. Mice were trained in a head-fixed whisker detection task in which they reported whisker deflection by licking during a 1-s response window. Infraorbital input removal opened a transient thalamocortical plasticity window in layer 4 of barrel cortex that peaked at postoperative day 17. During this window, mice showed faster acquisition and improved detection of near-threshold whisker stimuli. Electrophysiological recordings revealed enhanced layer 4 cortical encoding at low stimulus intensities, driven primarily by stronger neural activity and a higher fraction of trials with sensory-evoked responses. Local blockade of GluN2B-containing NMDA receptors reduced both thalamocortical potentiation and the associated behavioral advantage, indicating that GluN2B-dependent signaling is required for the enhanced learning state. Behavioral training also reshaped the plasticity window. Training initiated before or during the window advanced or prolonged thalamocortical potentiation, whereas training after window closure failed to reinstate it. The same temporal rules predicted long-term memory retention. These findings suggest that reactivated thalamocortical plasticity after peripheral input loss is not merely compensatory, but can enhance perceptual learning and memory in the adult brain.

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Poster

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Topic: E.02. Somatosensation – Touch

Support: NIH R15MH124042

Title: Perineuronal Net Degradation in the Primary Somatosensory Cortex Impairs Early Maternal Learning in Female Mice

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Abstract: Adaptive maternal behavior requires experience-dependent plasticity within sensory circuits that guide pup-directed actions. Perineuronal nets (PNNs), specialized extracellular matrix structures that primarily surround parvalbumin-positive interneurons, regulate cortical plasticity associated with maternal experience. Previously, we found that pup retrieval experience was associated with increased PNN expression in the right primary somatosensory cortex (S1) barrel field (BF) of adult wild-type female mice (WT). In contrast, naïve Mecp2-heterozygous females (Het), a model of Rett syndrome, exhibited elevated PNN expression in both S1BF hemispheres relative to naïve WT. These findings suggested that dynamic regulation of PNNs within S1BF may support WT maternal learning, whereas aberrant PNN expression contributes to impaired retrieval behavior in Het. To directly test the functional role of S1 PNNs in maternal learning, WT and Het received injections of chondroitinase ABC (ChABC) or vehicle (n =15 per group) into right S1BF and both S1BF, respectively. Pup retrieval performance was assessed across six daily testing sessions and analyzed using mixed-effects model. ChABC treatment significantly altered WT learning trajectories (group × session interaction: $F(2,305.6)=9.50$, $p<0.0001$). They displayed longer retrieval latencies during the first three days than control group. These differences were resolved later days. In contrast, although Het also improved across days ($F(1,273.48)=30.87$, $p<0.0001$), ChABC-treated Het did not significantly affect retrieval latency trajectories (group × session interaction: $F(2,273.50)=0.13$, $p=0.876$). Histological analyses confirmed successful degradation of PNNs throughout the primary somatosensory cortex. Notably in WT the extent of PNN degradation within the AP range spanning +0.75 to −0.25 mm from bregma was significantly correlated with individual learning rates, indicating that disruption of specific somatosensory cortical territories predicts behavioral outcome. These findings demonstrate that PNNs in the right hemisphere of rostral S1 mediates the acquisition of WT maternal behavior. The absence of comparable effects in Het suggests that mechanisms of cortical plasticity regulated by PNNs may already be altered in the Mecp2-deficient brain. Together, these results identify a role for somatosensory extracellular matrix regulation in maternal learning and provide insight into plasticity mechanisms relevant to neuropsychiatric disorders.

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Poster

PSTR272: Barrel Cortex

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BBRF Young Investigator Award to Alicia Che
Department of Mental Health and Addiction Services or the State of Connecticut

Title: Oxytocin mediates the emergence of social touch representation in the developing cortex

Authors: *L. LIN[1], I. NWABUDIKE[1], Y. ZHANG[2], R.-J. LIU[1], R. C. FROEMKE[3], N. DE MARCO GARCIA[4], S. SAXENA[2], A. CHE[1];
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Abstract: A central challenge in studying social behaviors is determining how the brain integrates social context with sensory processing. While primary somatosensory cortex (S1) was traditionally thought to process only physical attributes of touch, converging evidence suggests S1 also encodes social attributes of touch. In rodents, whisker-mediated facial touch is a predominant modality of social interaction, represented by S1 barrel cortex. S1 barrel cortex circuitry matures during the third postnatal week, a period when social contact with the dam is critical for neonatal survival. We asked how social touch representations in S1 emerge during this developmental window, and what molecular signals drive this process. The neuropeptide oxytocin (OXT), with its well-established role in social behavior and growing implication in sensory cortex modulation, is a prominent candidate.To investigate social touch representation in S1, we designed a longitudinal head-fixed 2-photon imaging setup to examine S1 neuronal activity in pups during dam-initiated whisker touches (naturalistic social touch). From the second to third postnatal week, touch-evoked activity clusters became progressively more distinct. To assess the effects of social context on controlled sensory stimulation, we also designed a setup to examine pup S1 neuronal activity during mechanical whisker stimulation while the dam is in close proximity (simulated social touch). We observed a small but consistent decrease in the proportion of responding neurons at P21, achieved by suppressing activation of less reliable and weakly responsive neurons. We also observed OXT release in pups during dam presence, and social modulation of sensory representation was recapitulated by oxytocin receptor (OXTR) agonist or abolished by OXTR antagonist. OXTR expression in S1 is largely restricted to somatostatin (SST) interneurons and pyramidal neurons, and OXT modulates these populations through distinct mechanisms. OXT increases SST interneuron excitability to enhance inhibitory tone, promoting sparse coding and sharpening sensory responses in social context. In pyramidal neurons, oxytocin-mediated synaptic plasticity selectively enhances activation to social contexts. Together, our findings identify a cell-type-specific mechanism by which OXT shapes social touch representation in S1, providing a biological basis for how neuromodulatory signals integrate social context with sensory processing during a critical developmental period.

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Poster

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Support: EMBO Postdoctoral Fellowship (ALTF 563-2024)
Academy of Medical Sciences Professorship (APR6\1007)
Wellcome Trust Discovery Award (225210/Z/22/Z)

Title: Learning rapidly reshapes topographic representations in sensory cortex

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Abstract: Learning can reshape sensory receptive fields, but whether it can rapidly reorganize topographic maps remains unclear. Previous work from our lab demonstrated learning-dependent reorganization of whisker primary somatosensory cortex (wS1), suggesting that behavioral demands can reshape somatotopy itself. Here, we tested whether such reorganization can emerge over only a few days of learning. We developed a whisker-based Pavlovian task in which mice learned to distinguish concave from convex shapes. Mice acquired the task within 8-15 days, exhibiting anticipatory licking to rewarded but not unrewarded shapes. Lesions of wS1, but not neighboring cortex, reduced performance to chance, demonstrating wS1 involvement in the task. To track learning-related changes in neural activity, we chronically implanted multi-shank silicon probes in wS1 and recorded single units from cortical columns representing 2-3 facial whiskers throughout learning. Behavioral decoding revealed that whisker kinematics and contacts predicted both stimulus identity and choice, with the number and duration of C2 whisker contacts contributing most strongly to discrimination performance. In naïve sessions, neurons responded most strongly to contacts made by the whisker corresponding to their recorded cortical column, consistent with somatotopic organization. Following learning, neurons across columns shifted from encoding their topographically matched whisker to preferentially encoding contacts made by the behaviorally informative C2 whisker. In parallel with the reorganization of somatotopic representation, learning altered the overall responsiveness of wS1 neurons. Across all stages of learning, many neurons responded to shape contact, and a subset showed selectivity for the rewarded shape. In contrast to reports of enhanced responses to rewarded stimuli during learning, we observed a progressive reduction in the fraction of contact-responsive and reward-selective neurons, as well as contact-evoked and reward-selective firing-rate gain. These findings demonstrate that topographic representations in primary sensory cortex can be reshaped within days to preferentially represent task-relevant sensory information. Paradoxically, this reorganization was accompanied by reduced neuronal responsiveness and selectivity. Learning may shift sensory processing from distributed representations of stimulus identity toward enhanced representation of the sensory features that are most informative for behavior, enabling more efficient discrimination.

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Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

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Program #/Poster #: PSTR272.10/CC16

Topic: E.02. Somatosensation – Touch

Title: Utilizing Conditioned Place Preference to Assess Tactile Threshold of Whiskers in Wildtype, Barrelless, and Prrxl1 KO Mice

Authors: *C. NARCISO[1], G. LI[2], G. CATALDO[3], J. C. BRUMBERG[4];
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Abstract: In humans, the somatosensory system is responsible for processing touch, a sense that we rely on for everyday life. Damage to this system affects a sizable portion of the population, approximately 15% which can lead to loss of sensation, and even neuropathic pain. In 2011, the Kennedy lab devised the Bumps test, a sensitive method of quantifying somatosensory thresholds in human fingers for the early detection of peripheral neuropathy. However, no such method currently exists for mice. The barrel cortex in mice processes tactile information from the whiskers (functionally analogous to fingers in humans), which are used to navigate the environment. In this study, we developed a method to quantify the tactile sensory threshold of the whiskers, as mice are commonly used in translational research. In order to assess threshold, we used Conditioned Place Preference (CPP), a paradigm where animals learn to associate a particular environment with a reinforcer to discriminate between progressively finer textures. The rodent trigeminal system has been implicated in a variety of active sensing behaviors including texture discrimination where the absence of patterning is associated with disruption of these behaviors. We used wildtype (WT), barrelless (BRL), and Prrxl1 knockout (KO) mice. BRL mice lack the typical cortical patterning in the barrel cortex whereas KOs lack patterning throughout the pathway from the whiskers to the barrel cortex. Our behavioral CPP paradigm occurred over 5 days. On day 1, mice were acclimated to a clear plastic arena, lined with smooth, black acrylic panels. On day 2, mice were assessed for pre-bias/innate preference by being placed in an open arena lined on the inside with smooth black panels (0 μm) on one half/side and rough black panels (~50 μm) on the other half. On days 3-4, mice were conditioned to associate either the smooth or rough texture to a 15% sucrose solution, immediately followed by preference testing on day 5. All sessions lasted 30 minutes, with days 1-4 having 2 sessions (morning/afternoon) and day 5 having only 1 session. Behavior was recorded with an infrared camera in the dark and analyzed using a Noldus computer system with Ethovision XT 16 software. Results showed that WT, BRL, and KO mice were able to be conditioned to a texture, specifically, the rough ~50 μm texture. To further investigate tactile threshold, mice were tested with finer ~10 μm panels using the same behavioral paradigm and set up. Results of using the finer panels showed that Prrxl1 KO mice were unable to associate the finer texture with the sucrose solution, indicating that the absence of patterning significantly impacts their ability to discriminate between textures.

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Poster

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Topic: E.02. Somatosensation – Touch

Support: FamilieSCN2A Action Potential Award
R01MH125978

Title: Examining Scn2a loss-of-function in sensory perception

Authors: *K. A. SALVATI[1], R. ALEXANDER[2], E. HAMADA[3], D. FELDMAN[4], K. J. BENDER[2];
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Abstract: 90% of people with autism spectrum disorder (ASD) exhibit atypical sensory processing. Changes in tactile sensitivity, altered tactile detection, and attention to specific sensory stimuli are well documented, but the cellular and circuit mechanisms that underlie these alterations are not well understood. One hypothesis for a central locus that modulates tactile processing is the primary somatosensory cortex (S1). In S1, layer 5 (L5) pyramidal neurons (PYR) act as coincidence detectors: integrating "bottom-up" subcortical sensory information and top-down "higher-order," contextual input at the basal and apical dendrites, respectively. This integration is critical for conscious perception, and studies have suggested that loss of L5 PYR coincidence detection corresponds to loss of consciousness with anesthesia. Thus, L5 PYR functional deficits may cause a breakdown in sensory perception, a hypothesis associated with atypical tactile sensitivity in ASD. Our lab has shown that L5 PYR function depends on *Scn2a*, and that *Scn2a* haploinsufficiency diminishes dendritic excitability. Herein, we investigate whether *Scn2a* haploinsufficiency affects sensory perception. We trained wild type (WT) and *Scn2a*$^{+/-}$ mice to perform a Go/No-Go whisker detection task. In varying whisker deflection amplitude, psychophysical response curves were generated for WT and *Scn2a*$^{+/-}$ mice. Psychometric functions demonstrate that stimulus strength increases response probability in both WT and *Scn2a*$^{+/-}$ mice. However, *Scn2a*$^{+/-}$ mice show weaker responses at moderate-to-high amplitude whisker deflections and lower response probability at 50% and 100% max whisker deflection amplitude relative to WT mice. All suggest *Scn2a*$^{+/-}$ mice require more intense stimuli for detection, which reflects a considerable shift in their perceptual threshold. These data demonstrate that *Scn2a*$^{+/-}$ mice likely show reduced sensitivity to whisker deflection and a greater reliance on stronger stimuli to guide behavior. In parallel, we performed two-photon calcium imaging to capture S1 L5 PYR apical dendrite calcium responses to whisker deflections during the behavior task. Preliminary observations suggest that *Scn2a*$^{+/-}$ apical dendrite calcium signals have smaller amplitudes and are overall less tuned to principal whisker deflection relative to WT

mice. Currently, we are using Sim1-Cre::*Scn2a*$^{+/flx}$ mice to test the central hypothesis that impaired dendritic integration in pyramidal tract L5 PYR, specifically, is sufficient to impair sensory perception.

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Poster

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Topic: E.02. Somatosensation – Touch

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AFOSR FA9550-23-1-0701

Title: Depth-resolved Bessel-beam two-photon calcium imaging reveals distinct computational roles for Layers 2 and 3 during cortical learning

Authors: *S. KANT[1], S. YADAV[1], H. V. KERI[1], S. PLUTA[2], K. JAYANT[1,3];
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Abstract: The mammalian neocortex encodes sensory experience through laminar circuits, yet Layer 2/3 (L2/3) is conventionally treated as a unified computational unit despite its cytoarchitectural heterogeneity and depth-dependent connectivity. Here, we use volumetric two-photon Bessel-beam calcium imaging to simultaneously record hundreds of neurons across a 500×500×95 μm volume spanning L2/3 in the mouse barrel cortex, achieving depth reconstruction of recorded neurons with a 10 μm axial resolution during a two-whisker tactile discrimination go/no-go task. This approach eliminates the temporal and sampling biases inherent to planar or sequential sub-volume imaging, enabling accurate characterization of population codes and their evolution with learning. We find that sensory representations (online) and reactivation events (offline) vary systematically with cortical depth. Ensemble (co-active groups of neurons) size during both the online and offline phases decreases across L2/3 as learning progresses. In the Go barrel, this spatial compression is concentrated in Layer 2. Offline ensemble reactivations, predictive of the next immediate future trial outcome, increase in proportion to Layer 2 participation during-but not after-learning, thereby linking sublayer identity to consolidation dynamics. Layer 3 neurons, on the other hand, exhibited more offline reactivation dynamics during the expert phase. In the NoGo barrel, however, ensembles with greater L2 participation exhibited increased neuronal participation, indicating that omission-based reinforcement does not engage L2-dependent sparsity. Together, these findings reveal a functional dissociation within L2/3: Layer 2 drives spatial sparsening and temporal reactivation

over learning, while Layer 3 sustains distinct representational functions. These results reframe L2/3 as a heterogeneous structure whose sublayers make separable contributions to cortical learning.
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Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.13/CC19

Topic: E.02. Somatosensation – Touch

Title: Multi-dimensional Naturalistic Decision-making in a Tactile Virtual Reality

Authors: *S. ZHANG[1], A. G. ARMSTRONG[2], Y. VLASOV[3];
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Abstract: Perceptual decision-making paradigms typically utilize unnatural behaviors that require weeks of training and rely on learned, goal-directed actions influenced by rewards. To investigate the behavioral psychometric characteristics in ethologically relevant perceptual decision-making, we developed a tactile virtual reality to mimic the naturalistic whisker-guided navigation behavior of mice where the animals must make high speed decisions to turn left or right. Through multi-dimensional behavioral data analysis, we uncovered latent behavioral variables that correspond to precise decision epochs at ultra-localized timescales.
Here, mice are head-fixed on a suspended ball with a pair of walls positioned both sides of the mouse's snout, with the lateral movement of the walls controlled by a real-time VR system to guide navigation. In stark contrast to existing paradigms, the main session is unrewarded, not goal-directed, unfamiliar to the mice, and designed to simulate natural behavior of navigating left and right turns directed by sensing the approaching walls by their whiskers. Multiple body tracking cameras and one high-speed whisker tracking camera are set up to track and reconstruct the precise locomotion of the mouse as well as the sensory input reflected by the movement of whisker. We quantify turning success based on lateral distance change and calculate reaction times using multi-dimensional behavioral analysis. From this, we calculate two psychometric characteristics: (1) turning accuracy as a function of wall distance, (2) reaction time as a function of wall distance. The curve of accuracy and wall distance presents a classical Sigmoid function

indicating that the shorter the distance, the higher the success rate. The second curve shows that decision time is positively correlated with the wall distances, indicating that stronger stimuli leads to faster decisions. We show that the reaction time follows a skewed distribution and the variance becomes bigger under a weaker sensory input condition. These results are consistent with predictions of the traditional bounded integration decision model.
To uncover the neural correlates of these naturalistic decisions, we perform large scale acute electrophysiological recordings during active behavior. Two Neuropixels probes are inserted in primary somatosensory cortex and secondary somatosensory cortex simultaneously. Surprisingly, we find strong decision-related activity in recurrent feedback loops between these two regions. These results provide a unique opportunity to study the dynamics of cortico-cortical feedback loops during naturalistic perceptual decision-making.

Disclosures: S. Zhang: None. **A.G. Armstrong:** None. **Y. Vlasov:** None.

Poster

PSTR272: Barrel Cortex

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR272.14/CC20

Topic: E.02. Somatosensation – Touch

Title: Lateral Spread as a Novel Gain Mechanism in a Whisker-based Selective Detection Task

Authors: *S. KABBARA[1], E. ZAGHA[2];
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Abstract: Selective attention requires the nervous system to amplify behaviorally relevant sensory signals while suppressing irrelevant distractors. Mechanisms of sensory gain, such as pre-filtering through thalamic gating and center-response amplification, have been proposed to explain this selective tuning of sensory stimuli. However, prior widefield calcium imaging from our lab showed that target stimuli propagate broadly from the whisker area of primary somatosensory cortex (wS1) into downstream cortical regions, whereas distractor responses remain spatially restricted despite comparable initial sensory encoding in a whisker-based Go/NoGo selective detection task. Here, we propose lateral spread as a novel gain mechanism, where task-relevant stimuli recruit neighboring cortical regions to enhance signal propagation and distractor stimuli remain spatially constrained. Using body imaging and electrophysiological measures, we examined if target-based lateral spread is attributable to a sensory process rather than movement-based activity in the same Go/NoGo task. Firstly, through motion energy analyses, we found that whisker movement began approximately 100ms after stimulus onset and was aligned with the response. In contrast, electrophysiological recordings in wS1 showed that target-evoked activity emerged within ~10-15ms and propagated to a medial limb-region site 1.5 mm away by ~50ms. Importantly, this spread remained stimulus-aligned rather than response-aligned and occurred before the earliest detected whisker movement. These findings support a model in which lateral spread functions as a stimulus-driven mechanism for selectively

increasing cortical recruitment during target detection. By distinguishing lateral spread from whisking and licking, this work proposes that spatial propagation across somatosensory cortex is not a byproduct of movement, but instead a candidate mechanism by which the brain enhances relevant sensory information and routes it to downstream processing regions.

Disclosures: S. Kabbara: None. **E. Zagha:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.01/CC21

Topic: E.03. The Chemical Senses

Support: Intramural Research Program at the National Institute on Drug Abuse ZIA DA000642

Title: Nostril-specific odor representations in human olfactory cortex

Authors: *C. U. RAITHEL[1], R. SULLIVAN[1], J. WORTHY[1], G. N. DIKECLIGIL[2], T. KAHNT[1];
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Abstract: The human olfactory system receives sensory information from two anatomically distinct nostrils. Existing evidence on how these separate streams of information are processed in the human brain and used for behavior is inconclusive. In this study, we ask how the olfactory system encodes sensory inputs from the left and right nostril, and how both behavior and neural representations are influenced by stimulus laterality. For this purpose, we developed a novel olfactory perceptual decision-making task in which we deliver binary odor mixtures to the left or right nostril and ask participants to indicate the dominant component in the mixture. We simultaneously record brain activity using fMRI and measure nasal airflow in each nostril separately to account for differences in neural representations as a function of the nasal cycle. Our findings from N=21 (four sessions per subject) suggest that participants can successfully discriminate unilaterally delivered odor mixtures. Interestingly, although participants cannot reliably determine the site of odor stimulation (left vs. right nostril), fMRI responses in primary olfactory regions are highly lateralized, showing significantly stronger responses to ipsi- compared to contralateral odor delivery. Moreover, representational similarity analysis of multivoxel activity patterns shows that odor identity representations generalize across nostrils in orbitofrontal cortex (i.e., secondary olfactory cortex), but not in piriform cortex (i.e., primary olfactory cortex). These findings suggest that stimulus laterality differentially influences odor coding at different stages along the processing hierarchy and raise intriguing questions regarding the functional relevance of ipsi- vs. contralateral neural representations for odor-guided behavior.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.02/CC22

Topic: E.03. The Chemical Senses

Support: NIH Grant DC014701
NSF 49100425C0019

Title: Computational tradeoffs in olfactory bulb architectures across vertebrate clades

Authors: *G. MANOJ, T. A. CLELAND;
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Abstract: Olfactory bulb (OB) principal neurons receive synaptic input from primary sensory neurons within receptor-specific OB glomeruli. Vertebrates exhibit two distinct anatomical architectures at this interface: mammalian monoglomerular wiring, in which mitral cells sample from single glomeruli, and multiglomerular wiring, observed in non-mammalian tetrapods, in which mitral cells sample from multiple glomeruli, integrating input from multiple receptor channels. The computational principles underlying the evolutionary preservation of these divergent architectures remain unresolved. To investigate how glomerular convergence architecture shapes odor representations, we developed a large-scale computational OB model in which odor ligands exhibit receptor-specific affinities and efficacies, competitively bind receptors, and generate distributed glomerular activation patterns. Across 64,800 network configurations with 3 replicates each, we compared monoglomerular networks (CR1) against multiglomerular networks (CR4) while systematically varying receptor count, mitral cell count, odor complexity, synaptic weights, odor concentrations, and activation noise. To isolate intrinsic representational structure, networks were evaluated using non-parametric metrics, including k-nearest-neighbor classification and sparsity statistics. Increasing receptor diversity consistently improved odor separability and effective dimensionality, whereas increasing competitive receptor interactions reduced decodability. CR1 preserved sparse, high-contrast representations with improved geometric separability in low-noise regimes, whereas CR4 generated denser distributed representations and exhibited improved robustness under noisy conditions. Each of these two architectures was favored under different system constraints. In CR4 architectures (only), increasing mitral cell number strongly affected representational structure. Most importantly, overcomplete mitral cell populations (more mitral cells than receptor channels) increased effective dimensionality beyond that of the receptor layer, as measured by participation-ratio efficiency (>1.0), indicating that downstream population coding expanded the dimensionality of odor representations. This expansion was strongest at lower receptor diversities and higher mitral-to-receptor ratios. Overall, CR4 was advantageous given lower receptor diversity, whereas CR1 became more effective as receptor diversity increased under sufficiently low-noise conditions.

Disclosures: G. Manoj: None. **T.A. Cleland:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR273.03/CC23

Topic: E.03. The Chemical Senses

Support: NIH Grant DC014701
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Cornell Sage Fellowship

Title: Effects of associative conditioning on whole-brain odor representations

Authors: *T. WU, M. EINHORN, C. YANG, T. A. CLELAND;
Psychology, Cornell Univ., Ithaca, NY

Abstract: Odor-gated neural representations in the brain, rather than simply reflecting the physical properties of an external odor stimulus, are shaped by prior experience and acquired meanings, which determine the brain resources required to make appropriate decisions and behavioral responses. In order to directly measure the recruitment of diverse brain regions into constructed representations based on the previously learned associations of odor cues, we visualized immediate-early gene (IEG) expression activity (Fos and Npas4) at cellular resolution in intact, aqueously cleared mouse brains. Brains were imaged on a light sheet microscope; images then were registered to the Allen CCFv3 using a custom ANTs-based method and segmented with a Paxinos & Franklin-based 3D atlas. Labeled cells were identified by a custom model constructed with BrainGlobe Cellfinder tools. How do induced neuronal activation patterns in animal brains - as judged by IEG expression patterns - differ when presented with identical odorants previously associated with dissimilar consequences? In two separate studies using different transgenic reporter strains (FosTRAP;Ai14, Npas4-CreER;Ai14), we conditioned three groups of mice to associate the odorant 2-hexanone (at 1 Pa vapor-phase partial pressure) with different outcomes. In one group, odor was forward-paired with footshock; in a second group, odor was explicitly unpaired with footshock; in a control group, odor was presented without footshock. After two hours (short-term memory) or 24 hours (long-term memory), we presented 2-hexanone to the mice in a dissimilar context, and measured behavioral responses and IEG activation patterns in the brain. 4-hydroxytamoxifen injections to induce IEG labeling were delivered after behavioral testing. Using Annolid behavior analysis software, we tracked mouse movements and analyzed fear-related behaviors including instantaneous velocity (freezing), darting, and place preference across pre-odor, odor (presentation), and post-odor epochs. Only the forward-paired groups, at both latencies, exhibited significantly increased freezing compared to control groups during odor and post-odor epochs. No interactions were observed with IEG type (Fos vs Npas4) or sex. We present and compare counts of IEG-expressing neurons within

atlas-defined brain regions across all experimental groups using a DESeq2-based statistical strategy.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR273.04/CC24

Topic: E.03. The Chemical Senses

Support: NIH Grant DC014701
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Title: Cholinergic modulation of spike phase-locking to fictive odor-evoked gamma oscillations in olfactory bulb slices

Authors: *J. CUNNINGHAM, T. A. CLELAND;
Psychology, Cornell Univ., Ithaca, NY

Abstract: The circuitry of the mammalian olfactory bulb transforms broad patterns of chemosensory input, modulated on a behavioral timescale, into a new metric based on the regulation of principal neuron (MTC) spike timing on a gamma-band timescale (~30-80 Hz). We use multielectrode array recordings from olfactory bulb slices, together with optical stimulation patterns designed to mimic the spatiotemporal properties of odor sampling, to study this transformation in detail and with greater control over input properties than is possible in vivo. Here, we measure the effects of cholinergic neuromodulation on the construction of fine-timescale odor representations based on fictive odor inputs.
Horizontal olfactory bulb slices from OMP-ChR2-EYFP (ORC-M) transgenic mice were presented with spatiotemporal patterns of light stimulation designed to simulate a homologous series of sequentially similar odorant stimuli. During fictive odor presentations, gamma oscillations (30-80 Hz) were evoked both under control (CTRL) conditions and in the presence of 20 uM of the cholinergic agonist carbachol (CCH). Fictive odor stimulation induced a significant minority of MTCs, the identities of which corresponded to odor quality, to evoke spikes that were phase locked to gamma. Across all fictive odorants tested, we found that a greater proportion of MTCs were significantly phase-locked to gamma under CCH when compared to CTRL trials (i.e., exhibited significant Rayleigh PLV Z-scores, $p < 0.05$). Additionally, among significantly phase-locked units, MTCs individually were more sharply phase-constrained under CCH than under CTRL conditions, based on a phase-locking metric corrected for spike count biases ($Z(PLV) = 4.06$ for CTRL, 5.41 for CCH). Finally, channel codes for fictive odors, when defined by MTC pairwise phase consistency (PPC) values rather than spike rates (a measure unbiased by spike count), become progressively more decorrelated as the underlying fictive odorants become more dissimilar. These findings demonstrate that

cholinergic neuromodulation in the olfactory system has a consistent and corresponding effect on odor representations predicated on spike timing regulation and synchronization on the gamma timescale.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

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Title: From Common Input to Diverse Output: Correlative Functional and X-ray Imaging Reveals Structured Diversification Within Glomerular Output Channels

Authors: *Y. YANG[1], Y. ZHANG[1], T. ACKELS[1,2], S. KHAN[1], J. REICHMANN[1], S. TOOTOONIAN[1], C. DELLA CASA[1], A. LAUGROS[3], A. VOROBYEV[3], W. CHÈVREMONT[3], A. PATERA[4], K. DENISOVA[5], A. SVETLOVE[5], J. ALBERS[5], A. BONNIN[6], J. LIVINGSTONE[3], A. NATHANSEN[7], N. RZEPKA[7], F. MARBACH[1], P. CLOETENS[3], A. PACUREANU[3], C. BOSCH PIÑOL[1,4], A. T. SCHAEFER[1];
[1]Francis Crick Inst., London, United Kingdom; [2]Univ. of Bonn Med. Ctr., Bonn, Germany; [3]The European Synchrotron (ESRF), Grenoble, France; [4]ALBA Synchrotron, Cerdanyola del Vallès, Spain; [5]European Mol. Biol. Laboratory, Hamburg Unit c/o DESY, Hamburg, Germany; [6]Paul Scherrer Inst., Villigen-PSI, Switzerland; [7]scalable minds GmbH, Potsdam, Germany

Abstract: A central question in systems neuroscience is how populations of neurons transform shared input into diverse output representations. In the mouse olfactory bulb, dozens of mitral and tufted cells (MTCs) associated with a single glomerulus ("sister" cells) receive common sensory input, providing a model for studying how functional diversity emerges within a defined circuit module. Previous studies have reported conflicting conclusions regarding sister cell similarity and diversity, likely due to the limited number of identified sister cells available in each animal. Here, we combined large-scale in vivo two-photon calcium imaging (2P) with post hoc synchrotron microCT and targeted X-ray nanoholotomography (XNH) to identify glomerular affiliations of physiologically characterized MTCs in a high-throughput and unbiased manner. During functional imaging, mice were presented with large panels of odorants in awake and anaesthetised states, as well as multiple concentrations and temporal dynamics of selected odorants. XNH enabled dendritic tracing and identification of sister-cell relationships within the imaged tissue volume. We have collected seven correlative 2P-XNH datasets, each containing functional measurements from hundreds of MTCs associated with dozens of glomeruli, including individual glomeruli with >30 identified sister cells. We find that sister cells consistently exhibit more similar odour preferences than non-sister cells in both awake and anaesthetised animals, confirming that common glomerular input constrains functional tuning. At the same time, sister cells show substantial and robust diversity. This diversity is reproducible across repeated stimulus presentations, and patterns of cell-cell similarity within individual sister cell groups are preserved across wakefulness and anaesthesia, even when overall odour representations shifted between states. Furthermore, glomeruli differ in how sister-cell diversity varies with odour concentrations: some exhibit concentration-invariant differences, whereas others show concentration-dependent diversification. Together, these results reveal that common sensory input generates structured rather than redundant output representations. The persistence of sister-cell diversity across repeats, stimulus conditions, and brain states argues that it reflects an underlying circuit property rather than measurement noise. By linking large-scale functional characterization to anatomical identification of neurons, this work establishes a platform for uncovering structure-function relationships within neural populations at subcellular resolution.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.06/CC26

Topic: E.03. The Chemical Senses

Support: NSF (IOS-1355034)
NIH (P30AI117970)
Howard University College of Medicine

Title: Interactions of two neurotransmitter systems in the main olfactory bulb: metabotropic glutamate receptors and cannabinoid receptors

Authors: *T. HEINBOCKEL[1], Z. WANG[2];
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Abstract: Metabotropic glutamate receptors (mGluRs) have been implicated in several neurological diseases such as stroke, epilepsy, schizophrenia, Parkinson's and Huntington's disease. Endogenously released cannabinoids (endocannabinoids) have been shown to regulate neuronal activity. Here, we aimed to better understand how these two neurotransmitter systems, mGluRs and cannabinoid receptors, interact. Our previous data showed that exposing the olfactory bulb network to cannabinoid receptor antagonist, AM251, or mGluR antagonist, LY367385 alone, resulted in a decrease of mitral cell firing. Based on this data, our hypothesis was that exposure of mitral cells to both AM251 and LY367385 together would result in mitral cell firing to decrease even further. Patch-clamp electrophysiology was used to record from mitral cells. We found that the combined application of LY367385 and AM251 resulted in increased mitral cell firing. To determine whether this was due to glutamate or GABA, mitral cells were treated with the same protocol, but in addition Gabazine, a GABA-A receptor antagonist, was added. In the next phase, APV and CNQX (ionotropic glutamate receptor blockers) were added. In the presence of AM251, LY367385, and Gabazine, mitral cell firing increased. However, in the presence of AM251, LY367385, APV, and CNQX mitral cell firing decreased. Based on these findings, we concluded that the increased firing of mitral cells in response to a combination of AM251 and LY367385 was a glutamate-induced effect. By better understanding how the metabotropic glutamatergic receptor system and endocannabinoid receptor system interact, we will gain insight into how to enhance neuroprotective measures in combating mGluR-related neurodegenerative diseases.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.07/CC27

Topic: E.03. The Chemical Senses

Title: Expansion and sparse coding structure odor differentiability in the *Drosophila* olfactory circuit

Authors: *G. JEONG[1], K. CHOI[3], C. HYEON[4], J. JO[1,5,2];
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Univ., Seoul, Korea, Republic of; [3]Dept. of Biol. Sci., Keimyung Univ., Daegu, Korea, Republic of; [4]Ctr. for AI and Natural Sci., [5]Sch. of Computat. Sci., Korea Inst. for Advanced Study, Seoul, Korea, Republic of

Abstract: The Drosophila olfactory circuit transforms odor responses from a compact ORN representation into a sparse, high-dimensional Kenyon cell (KC) code. Here, we combined electrophysiological ORN responses with FAFB connectome-derived ORN-PN and PN-KC connectivity to project odor-evoked activity into KC space. After filtering weakly activating odorants and underrepresented chemical classes, we analyzed representations of 87 odorants. We found that the ORN-to-KC transformation increases pairwise odor differentiability, as measured by cosine distance, and that this improvement depends on the synergy between dimensional expansion and winner-take-all sparsification mimicking APL-mediated inhibition. Wasserstein-distance analysis showed that KC representations better separate intra-class from inter-class odor similarities, with near-optimal performance across a sparsity range consistent with experimentally observed KC activity. Hierarchical clustering further revealed that KC odor codes are more uniformly organized than ORN codes, yielding higher Shannon entropy. Finally, KC representations enhanced the separation of attractive and aversive odorants, suggesting that behaviorally relevant odor structure emerges before downstream mushroom body output processing.

Disclosures: G. Jeong: None. **K. Choi:** None. **C. Hyeon:** None. **J. Jo:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR273.08/CC28

Topic: E.03. The Chemical Senses

Support: R01DC017979

Title: Integration of Central Complex and non-Central Complex pathways for olfactory navigation in Drosophila melanogaster

Authors: *E. SAMARA, Y. ZAMAN, K. NAGEL;
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Abstract: Parallel sensorimotor pathways of different depths are a common feature of nervous system organization across species, but the function of these parallel pathways is unclear. In *Drosophila melanogaster*, olfactory information reaches pre-motor centers both through the navigation center, namely the Central Complex, and through pathways that bypass this structure. We are investigating the contribution of each of these pathways to odor-guided navigation behavior. Developmental lesions and optogenetic silencing experiments suggest that the Central Complex pathway is critical for straight wind-guided runs evoked by odor. In contrast, non-Central Complex pathways may generate patterns of egocentric slowing and turning that are

prominent at the offset of odor. By combining optogenetic manipulations of connectome-defined pathways with *in vivo* imaging during a virtual wind-guided olfactory navigation task, we expect to delineate the precise contribution of each pathway to olfactory navigation behavior. Our study will provide insight into how parallel pathways of different depths orchestrate a complex goal-directed behavior.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

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Title: Odor-evoked neural activation in the hypothalamic axis is increased in Kv1.3 -/- Mice

Authors: *M. COMPAGNO[1], D. A. FADOOL[2];
[1]Inst. for Mol. Biophysics, [2]Prog in Neurosci & Molec Biophys, Florida State Univ., Tallahassee, FL

Abstract: Due to the well-documented link between olfactory bulb activity and regulation of metabolism, we utilized Kv1.3-/- mice (KO; voltage-gated potassium channel KCNA3) to test for the presence of altered functional connectivity between the olfactory bulb and hypothalamus. Because KO mice are thin without caloric restriction, exhibit increased total energy expenditure, have supernumerary glomerular connections, and increased excitability of projection neurons from the olfactory bulb, we hypothesized they may have altered functional connectivity between these regions. Wildtype (C57BL6/J, WT) and KO mice (n=6/genotype) were odor stimulated with 1 υM isoamyl acetate using a custom olfactometer delivering cyclic stimulation, followed by traditional *c-fos* immediate-early gene immunohistochemistry. We found a genotype independent main effect of odor stimulation in the glomerular layer (2w ANOVA, $p = 0.019$). Within the mitral and granule cell layers, however, KO mice had increased odor-evoked *c-fos* labeling over WT (2w ANOVA, MCL: $p < 0.0001$; GCL: $p = 0.0002$). Brain-wide *c-fos* activation was mapped (n=3/genotype) using tissue clearing and lightsheet microscopy. Computed 3D *c-fos* density maps were generated using ClearMap and compared within genotype (Student's *t*-test). KO mice exposed to odor showed higher *c-fos* expression in numerous downstream targets compared to that of WT mice. *C-fos* expression was analyzed in several energy-sensing regions of the hypothalamus, including the paraventricular hypothalamus (PVH), the dorsomedial hypothalamus (DMH), and the arcuate hypothalamus (ARH). PVH *c-fos*

expression was markedly enhanced in KO mice, yielding an odor x genotype interaction (2w ANOVA, $p = 0.025$). In the DMH and ARH, *c-fos* expression remained elevated following odor-stimulation but was not increased in the KO mice. To probe identity of activated neurons in the PVH, we quantified *c-fos* and vasopressin or oxytocin double labeling with the PVH, but none were apparent. When WT mice were challenged with a moderately high-fat diet (32.5% kcal/fat) to induce obesity, while there was a 3.3x basal increase in PVH *c-fos* expression, odor-evoked activation of PVH neurons were not blunted by the obesity (Odor: $p < 0.0001$, Diet: $p < 0.0001$, Interaction: $p = 0.042$). Because diet-induced obesity has been shown to decrease *c-fos* activation in the olfactory bulb and reduce odor perception and electro-olfactogram amplitude, lowered odor sensitivity interestingly does not appear to disrupt PVH activation. Our study reveals a complex association between the olfactory bulb and energy regulating regions of the hypothalamus, which may not be metabolic state dependent.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

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Title: The Association of Odor-Evoked Vivid Memories and Odor Identification with Later Executive Function

Authors: *E. BURROWS[1], C. MURPHY[2];
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Abstract: Scent is known to have the ability to elicit strong memories and emotions. Olfactory dysfunction has also been associated with cognitive decline later in life. Many studies cite odor identification as a predictor of mild cognitive impairment (MCI) and dementia. For this analysis, we investigated whether the number of vivid memories evoked by odors would predict later performance on an executive functioning task. We used archival data from the Rancho Bernardo Study of Healthy Aging where participants' age ranged from 43.8 to 99.9. Over the span of 24 years these participants were tested in many areas including olfaction after visit 7 and cognitive functioning at visit 10 to determine the risk of dementia. Whether an odor evoked a vivid memory was measured using a sum of the responses to the question "Did the odor evoke a vivid memory?", odor identification by the sum of correct odor descriptions, and executive function by the Trail Making Test B. A preliminary regression was conducted to examine the association of

odor-evoked vivid memories and executive function. We found that the number of odor-evoked vivid memories did predict executive function in an unadjusted analysis (n = 583). After accounting for age, this association was no longer significant, suggesting that it is likely that age largely determined the relationship between odor-evoked vivid memories and executive function. This pattern was consistent when investigating each odor separately. Another regression was conducted to examine whether odor identification predicted later executive function. We found that odor identification did predict later executive function; and age remained the most predictive factor of later executive function. When the odor identification and the vivid memories variables were taken together, they were less predictive of later executive function than odor identification alone. The results suggest that the addition of the number of vivid memories evoked by an odor does not increase prediction of later executive function independent of age; but that odor identification is an independent, robust predictor of later cognitive function.

Disclosures: E. Burrows: None. **C. Murphy:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.11/DD1

Topic: E.03. The Chemical Senses

Support: SFB 1328

Title: ATP-dependent neuromodulation in the processing of olfactory sensory information

Authors: *S. SHAHMORAD[1], D. HIRNET[2], C. LOHR[3];
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Abstract: In the central nervous system, purinergic signaling modulates neuronal communication in a multitude of brain circuits such as motor control and sensory pathways. Here, we investigate the role of ATP in the processing of olfactory signals. Olfactory receptor neurons (ORNs) in the olfactory epithelium detect odors and project to the olfactory bulb, the first relay station in the brain of the olfactory sensory pathway. There, within separate processing units called glomeruli, the ORN axons release glutamate and ATP as co-transmitter onto dendrites of mitral cells (MCs), external tufted cells (eTC) and local interneurons. MC and eTC integrate excitatory input from ORNs and inhibitory input from local interneurons to shape the output of the olfactory bulb encoding odor features, which then are interpreted by higher ordered cortical areas. Using patch-clamp recording of mitral cells in acute brain slices revealed that the local release of ATP from caged ATP in the glomerulus significantly depolarizes mitral cells, with the selective P2Y1 antagonist MRS2179 reducing strongly the ATP response. Therefore, mitral cells (MCs) in the olfactory bulb are modulated by ATP/ADP through a P2Y1 receptor-

dependent pathway. Approximately 75% of ATP-induced MC excitation was reduced in the presence of glutamate receptor blockers, whereas the ATP-response of eTC was far less sensitive to glutamatergic block. In contrast, application of TTX suppressed the ATP response in MC as well as in eTC, suggesting a P2Y1R-positive neuron is excited by ATP upstream of MC and eTC. In line with this, recording MCs of mitral and tufted cell- specific P2Y1R knockout animals showed no reduction in the ATP-response compared to wildtype littermates. The glutamatergic component of MC excitation most likely is exclusively based on the eTC-MC feed-forward mechanism, since depleting P2Y1R in other glutamate-releasing cells in the OB (olfactory sensory neurons, vGlut2(+) cells as well as astrocytes) using cell type-specific P2Y1 knockout animals showed no reduction in the ATP-response of MC. In conclusion, in the processing of olfactory sensory signals, release of ATP induces a multistep neuronal pathway eventually leading to glutamatergic feed-forward excitation of MCs which might enhance the response to weak odor signals.

Disclosures: S. Shahmorad: None. **D. Hirnet:** None. **C. Lohr:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.12/DD2

Topic: E.03. The Chemical Senses

Support: ROO DC017754
RO1 DC023915

Title: The medial AON is a recurrent associational cortex embedded within the olfactory system.

Authors: *Z. A. FYKE[1], J. D. ZAK[2];
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Abstract: The physiological organization of synaptic inputs and local circuitry within the anterior olfactory nucleus (AON) remains poorly understood despite decades of anatomical investigation (Schoenfeld & Macrides., 1984). Previous work has demonstrated that contextual information from the ventral hippocampus (vHPC) activates the medial AON (mAON) and is required for contextual olfactory-memory formation (Aqrabawi et al., 2020). We therefore hypothesized that the mAON functions as an associative cortical region that integrates both sensory and contextual input streams. To test this hypothesis, we injected the vHPC of mice with AAV9-ChR2-mCherry to enable optical control of projections to the mAON in acute brain sections. Whole-cell voltage-clamp recordings revealed both excitatory and inhibitory postsynaptic currents (EPSCs/IPSCs) in the mAON driven by light stimulation of vHPC inputs. EPSCs exhibited short onset latencies consistent with monosynaptic glutamatergic input, whereas IPSCs were significantly delayed (EPSC latency = 2.42 ± 1.12 ms, n = 27; IPSC latency

= 3.97 ± 0.62 ms, n = 7; p = 0.0049, Mann-Whitney U). Gabazine abolished IPSCs, indicating that vHPC excitation recruits local interneurons that mediate disynaptic inhibition. In current-clamp recordings, activation of vHPC terminals induced coordinated spiking activity across mAON neurons. However, preliminary data show pyramidal neurons exhibited prolonged suppression following initial activation, whereas interneurons showed sustained excitation, consistent with strong recurrent inhibitory control of principal cell activity. Finally, we examined the integration of sensory and contextual input streams in the mAON. Electrical stimulation of the lateral olfactory tract (LOT) failed to evoke monosynaptic excitatory post-synaptic potentials (EPSPs) or drive spiking in mAON cells, whereas optical activation of ChR2-vHPC terminals reliably drove spiking across cell types (spike probability, pyramidal cells: LOT stimulation = 0.0010, n = 15; vHPC stimulation= 0.432, n = 15). Together, these findings suggest that mAON receives sparse direct olfactory input but robust excitatory drive from the hippocampus. In addition to direct glutamatergic input from the vHPC, the mAON receives sparse input from the LOT, which drives dense recurrent inhibition that strongly regulates pyramidal neuron activity. These findings identify the mAON as a physiologically distinct associational subdivision of the olfactory cortex and provide a circuit-level mechanism through which contextual information may shape olfactory context representations and perception.

Disclosures: Z.A. Fyke: None. **J.D. Zak:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.13/DD3

Topic: E.03. The Chemical Senses

Support: NIH BRAIN 1R01NS111673
NIH TR01 5R01DC017876

Title: Brain-wide projection mapping of olfactory bulb output neurons by glomerular and receptor identity

Authors: *Z. DAWOOD[1], A. SUNDARARAJAN[1], K. SCHOENBERG[1], C. SOITU[1], A. BECALICK[2], P. ZNAMENSKIY[2], A. M. ZADOR[1], A. KOULAKOV[1], D. F. ALBEANU[1]; [1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]The Francis Crick Inst., London, United Kingdom

Abstract: The prevailing hypothesis for olfactory processing has assumed that sensory cortical representations lack structure and arise from randomly connected circuits. Using high-throughput, DNA barcode sequencing-based single-cell projection mapping methods (MAPseq and BARseq), we monitored the projection patterns of thousands of neurons in individual mice. We discovered that mitral cells of the olfactory bulb (OB) tile the anterior-posterior (AP) axis of the piriform cortex and project to extra-piriform bulb target regions, such as the anterior

olfactory nucleus, cortical amygdala, and lateral entorhinal cortex, in coordination with their cortical targets, thereby forming triadic circuit motifs. This body of work indicates that OB projections and the architecture of the olfactory cortex are structured, and that models of olfactory computation need not rely on assumptions of random connectivity (Chen et al., 2022 Cell). Mitral and tufted cells (MTCs) sharing a parent glomerulus (called sisters) form segregated modules. Here we build on our previous work to investigate the interplay between structure and randomness in the MTC long-range projections as a function of their 1) odorant receptor (OR) identity and responses to odorants, and 2) sister versus non-sister module identity. We injected barcoded Sindbis virus targeting the mitral cell layer along the AP axes of the mouse OB. Using BARseq 2.0, we performed *in situ* sequencing on 20 µm thick OB slices to trace barcodes from MTC somata to the apical dendrites to identify the parent glomerulus and sister cells. In the same experiment, we are also able to label each glomerulus by its OR identity using OR gene specific probes (11,244). We then performed MAPseq to reconstruct brain-wide projections of sister and non-sister MTCs (slicing the brain along the AP axes at 200 µm resolution) and investigated whether MTCs linked to a glomerulus target distinct cortical areas reproducibly and non-randomly across animals. We analyzed projection patterns by glomerulus, OR subfamily (Class I, II, TAAR), and ethological relevance. Across two animals, we barcoded 4,433 MTCs and identified sister sets. Our OR probes detected 504 unique ORs *in situ*, matching recent OR maps. Spatial analysis confirmed dorsal bias for Class I ORs and broader distribution for Class II ORs. These data enable the construction of high throughput glomerulus-to-cortex and OR-to-cortex projection matrices as well as relating them to the statistics of odorant responses. Together, our approach bridges molecular, anatomical and functional domains of the olfactory system and sheds light on how odor representations are structured at the neural circuit level.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.14/DD4

Topic: E.03. The Chemical Senses

Title: Targeting morphologically distinct subpopulations of olfactory output neurons constrained by molecular types and projection targets

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Abstract: Current models of mammalian olfaction posit that distinct olfactory bulb (OB) output neurons extract different odor stimulus features and transmit them in parallel to downstream

olfactory cortices. Recent evidence suggests that the two broad classes of output neurons, namely, mitral and tufted cells (MTCs), which are distinguished by morphology, connectivity, and physiology show further heterogeneity. A key prerequisite for understanding their role in olfaction is the ability to selectively manipulate these MTC subpopulations. We combined Cre-dependent expression with retrograde labelling in olfactory cortices to target MTC subpopulations. Cre-dependent AAVrg-Flex-Rpl22HA-eYFP was injected into six olfactory cortical regions in 8-10-week-old male and female Tbx21-Cre and Cck-Cre mice: AON pars externa (AONpe), AON ventrolateral (AONvl), cap of the olfactory tubercle (OTcap), anterior piriform cortex (aPCx), posterior piriform cortex (pPCx), and cortical amygdala (cAmyg). We found that, even for the same projection targets, injections in Cck-Cre vs. Tbx21-Cre mice label morphologically distinct MTC subpopulations in the OB. AON injections in Cck-Cre mice resulted in more bias towards superficially located tufted cells relative to Tbx21-Cre mice for both targets [percentage of labelled somata in superficial EPL for AONpe : 55.34 ± 10.51% (n=11 OBs) vs. 32.11 ± 4.83% (n=9 OBs), Welch's t-test, $P = 1.06 \times 10^{-5}$; and AONvl : 44.16 ± 8.01% (n=10 OBs) vs. 32.68 ± 4.43% (n=8 OBs), P = 0.0017]. OTcap injections biased labelling toward deep somata in both lines [somata in deep EPL for Cck-Cre : 76.11 ± 12.27% (n=9 OBs) and Tbx21-Cre : 85.53 ± 6.80% (n=9 OBs)], but in Cck-Cre, labelled lateral dendrites were mainly found in the middle EPL. Posterior targets labelled primarily deep MTCs in both Cck-Cre [somata in deep EPL for pPCx : 90.90 ± 8.76% (n=6 OBs); cAmyg : 89.84 ± 3.77% (n=5 OBs)] and Tbx21-Cre [somata in deep EPL for pPCx : 93.47 ± 2.42% (n=8 OBs); cAmyg : 94.08 ± 3.26% (n=6 OBs)]. However, posterior labelling tended to be sparser in Cck-Cre mice than in Tbx21-Cre mice [mean number of labelled cells in deep EPL for pPCx : 63.83±46.68 (n=6 OBs) vs. 177.75±32.78 (n=8 OBs); and cAmyg : 62.40±52.83 (n=5 OBs) vs.162.67±73.47 (n=6 OBs)]. These results demonstrate that projection mapping combined with Cre-dependent expression can selectively target morphologically distinct MTC subpopulations. We are using this approach to characterize the functional properties and gene expression patterns of these projection- and molecularly defined OB output neurons.

Disclosures: S. Nath: None. **I. Fukunaga:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.15/DD5

Topic: E.03. The Chemical Senses

Support: NIDCD R01 018075

Title: Time-course of odor coding in the human brain - a single-neuron perspective

Authors: *G. N. DIKECLIGIL[1], M. S. KEHL[3], J. A. GOTTFRIED[2], F. MORMANN[4]; [2]Dept. of Neurol., [1]Univ. of Pennsylvania, Philadelphia, PA; [3]Exptl. Psychology, Univ. of Bonn & Oxford, Bonn, Germany; [4]Univ. Clin. of Bonn, Bonn, Germany

Abstract: Odor information arising from the olfactory bulb is projected in parallel to the piriform cortex, amygdala, entorhinal cortex, and other sub-regions of the primary olfactory cortex. These brain areas, which receive direct monosynaptic input from the olfactory bulb, are highly interconnected and functionally linked to higher-order regions, including the hippocampus. However, the precise latency and temporal evolution of odor coding within and across these regions in the human brain remain largely unexplored. To address this, we conducted single-neuron recordings in epilepsy patients undergoing invasive intracranial seizure monitoring with Behnke-Fried electrodes. We recorded neural activity from the piriform cortex, amygdala, entorhinal cortex, hippocampus, and parahippocampal cortex (1230 units across 18 sessions) during an odor identification task in which short, 200-ms odor pulses were delivered via a computer-controlled olfactometer. Odors were delivered using a closed-loop system at consistent phases of the inhalation cycle to ensure temporal precision. Preliminary results show that neurons in the piriform cortex neurons exhibit the earliest and strongest odor responses and that a higher proportion of piriform neurons are modulated by odors compared to the amygdala, entorhinal cortex, hippocampus, and parahippocampal cortex. At the level of the population activity, we observed that the human olfactory network exhibits both rapid and sustained odor coding lasting ~7 seconds after odor presentation. Together, these initial findings demonstrate rapid and precise processing of complex odors by neurons in human olfactory network, laying the foundation for exploring interregional transmission and temporal dynamics in the human brain.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR273.16/DD6

Topic: E.03. The Chemical Senses

Support: NIH Grant 1RF1NS133598

Title: Asymmetrical strategies for olfactory discrimination tasks with symmetrical reward contingencies

Authors: *Z. WANG, K. M. WILLIAMS, A.-M. M. OSWALD;
Univ. of Chicago, Chicago, IL

Abstract: Mice encounter and discriminate mixtures of odorants in their living environment. In a foraging task, we trained the mice to discriminate two highly-overlapping mixtures with one of them containing a differentiating component. We found that mice select the differentiating component to solve the task when the mixture with the differentiating component is rewarded. However, mice do not use the differentiating component to solve the task when the mixture

without the differentiating component (i.e., the background mixture) is rewarded. These results suggest that tasks with symmetrical reward contingencies can give rise to asymmetrical perceptual strategies, i.e., feature selection when the differentiating component is associated with reward, and mixture selection when it is not. We perform acute electrophysiological recording in the anterior Piriform cortex (aPCx) of mice to investigate the cortical representations of asymmetrical strategies.

Disclosures: Z. Wang: None. **K.M. Williams:** None. **A.M. Oswald:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

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Program #/Poster #: PSTR273.17/DD7

Topic: E.03. The Chemical Senses

Support: NIH Grant 1RF1NS133598

Title: Reward-gated disinhibition of the piriform cortex across learning

Authors: *K. M. WILLIAMS, Z. WANG, A.-M. M. OSWALD;
Neurobio., The Univ. of Chicago, Chicago, IL

Abstract: Learning to associate sensory cues with reward requires modulation of cortical circuits that transform sensory input into behaviorally relevant representations. Although synaptic plasticity mechanisms have been extensively characterized, a central gap remains in our understanding of how reinforcement signals dynamically engage cortical microcircuits to permit learning in vivo. Previous work in our lab has demonstrated the role of somatostatin (SST) interneurons in the regulation of associative long-term potentiation in the anterior piriform cortex (aPC) in vitro; however, the dynamics of SST interneuron activity in the aPC across learning in behaving animals has not yet been investigated. In this study, we aim to characterize the dynamics of SST activity across discrimination learning to determine reward related modulations. SST-cre/Ai32 mice aged P60-80 were trained on a Stop/No-Stop olfactory discrimination running task. Neural recordings from Layer 2/3 of aPC were obtained using a 32-channel silicon probe with an integrated light fiber for optotagging SST interneurons. We initially trained mice on a simple odor association to learn the task itself and then trained on a CS+ and CS- odor discrimination paradigm. SST interneuron temporal response properties are characterized over the course of behavioral trials, during rewarded and unrewarded trials, and across learning during the odor discrimination paradigm. SST interneuron modulation is strongest during early learning when new odor representations are being established and decrease as animals reach expert performance. Changes in SST activity are expected to influence the formation and stabilization of odor-evoked ensemble representations. To examine this relationship, pyramidal neuron responses that were recorded on the same probes will be analyzed in parallel with SST activity. Pyramidal neuron tuning, response reliability, and selectivity for

rewarded versus unrewarded odors will be quantified across learning. Changes in SST reward modulations are expected to correlate with the emergence and stabilization of odor representations, and final data analysis will characterize SST and pyramidal neuron co-activity. These results help define how SST interneurons in the aPC are dynamically regulated across learning in behaving animals.

Disclosures: K.M. Williams: None. **Z. Wang:** None. **A.M. Oswald:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

Support: NIH Grant 1RF1NS133598

Title: Orbitofrontal cortex (OFC) provides broad subthreshold input to anterior piriform cortex (APC) that engages heterogeneous local inhibitory circuitry

Authors: *C. SUN, A.-M. M. OSWALD;
The Univ. of Chicago, Chicago, IL

Abstract: Top-down projections from orbitofrontal cortex (OFC) convey contextual and reward-related information to sensory cortex, but how these signals shape anterior piriform cortex (APC) circuitry remains unclear. A central question is whether OFC selectively targets specific interneuron populations to gate cortical activity, or whether selective representations emerge locally from recurrent circuit dynamics downstream of broad contextual input. To address this, we expressed channelrhodopsin-2 (ChR2) in CaMKIIa-positive glutamatergic neurons in ventral OFC of male and female mice and performed whole-cell patch clamp recordings in acute brain slices 3 weeks post injection. Recordings were obtained from vasoactive intestinal peptide (VIP), somatostatin (SST), and parvalbumin (PV) -expressing interneurons in APC identified by fluorescent reporters, as well as pyramidal neurons identified morphologically. OFC axon terminals were optogenetically stimulated during voltage- and current-clamp recordings using potassium- and cesium-based internal solutions. In a subset of experiments, VIP interneurons were chemogenetically suppressed using inhibitory DREADDs and deschloroclozapine (DCZ). OFC stimulation evoked excitatory postsynaptic currents (EPSCs) across all recorded cell types with broadly similar onset timing and temporal dynamics, consistent with distributed excitatory targeting. Despite widespread excitation, most neurons remained subthreshold following OFC stimulation alone. In contrast, inhibitory postsynaptic currents (IPSCs) were robustly recruited throughout APC, suggesting engagement of local recurrent inhibitory circuitry. IPSCs exhibited substantial heterogeneity across cells and recording conditions. Cesium-based recordings revealed larger EPSCs in interneurons relative to pyramidal neurons, consistent with differences in dendritic filtering or intrinsic integration properties, but did not reveal strong cell-type-

selective OFC targeting. Ongoing chemogenetic experiments are testing the contribution of VIP-mediated local circuit interactions to OFC-evoked inhibitory recruitment. These findings support a model in which OFC provides broad, largely subthreshold contextual feedback excitation to APC, while local recurrent circuitry and intrinsic neuronal heterogeneity transform distributed top-down input into selective cortical ensemble activity. More generally, weak top-down signals may bias, rather than directly dictate, sensory cortical representations.

Disclosures: C. Sun: None. **A.M. Oswald:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR273.19/DD9

Topic: E.03. The Chemical Senses

Support: Schmidt Sciences Foundation
NIH: 1R01DC020892
NSF: 2223839
NSF: 2323241
NSF: 2217058

Title: Recovering Circuit Plasticity from Neural Dynamics: Validation of Recurrent Neural Network Inference from a Biophysical Model of Associative Learning

Authors: *G. NAVAS[1], S. JOSHI[3], G. MISHNE[4], M. V. BAZHENOV[2];
[2]Dept. of Med., [1]UCSD, La Jolla, CA; [3]Univ. of California San Diego, San Diego, CA; [4]UC San Diego, La Jolla, CA

Abstract: Understanding the synaptic changes that enable rapid, generalizable learning remains a central challenge in neuroscience. Direct measurement of learning-induced connectivity changes is often impractical, whereas neural activity recordings are increasingly available. Recurrent neural networks (RNNs) provide a potential bridge between these levels of description by inferring the connectivity that best reproduces observed neural dynamics. By fitting RNNs to neural activity recorded before and after learning, it may be possible to identify candidate sites of plasticity from changes in inferred connectivity. However, the accuracy and limitations of this approach remain poorly understood. To evaluate this framework, we trained RNNs on synthetic neural recordings generated by a biophysically realistic model of the honeybee antennal lobe undergoing associative conditioning. Because the ground-truth connectivity of the model is known, inferred and actual synaptic weights can be directly compared. The RNN consisted of 100 excitatory projection neurons (PNs) and 280 inhibitory local neurons (LNs), matching the population sizes of the biophysical model and cell-type proportions of the in vivo antennal lobe. Networks were trained to reconstruct neural activity before and after conditioning from varying fractions of observed neurons. The RNN accurately reproduced single-neuron activity, achieving

higher correlations with the original traces than reference controls based on identity-shuffled ground-truth recordings. Accurate reconstruction was obtained not only for observed neurons but also for unobserved PNs, even when only 25% of neurons were available during training. Consistent with the biophysical model, where plasticity is restricted to inhibitory synapses, inferred connectivity captured an overall increase in inhibitory synaptic strength following conditioning. Furthermore, selectively preventing inhibitory weight changes between pre- and post-conditioning states in the RNN impaired activity reconstruction substantially more than preventing excitatory weight changes. This correctly identified inhibitory plasticity as the primary mechanism underlying learning-induced changes in network dynamics. These results demonstrate that mechanistic RNN models can recover biologically meaningful patterns of synaptic plasticity from neural activity alone. By integrating neural recordings with interpretable AI models, this approach offers a powerful framework for identifying the circuit mechanisms of learning and for uncovering general principles underlying associative and generalizable learning.

Disclosures: G. Navas: None. **S. Joshi:** None. **G. Mishne:** None. **M.V. Bazhenov:** None.

Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

Support: NIH: 1R01DC020892
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Schmidt Sciences Foundation

Title: Inhibitory Circuit Architecture Drives Sparse Traveling Waves for Odor Coding in the Locust Antennal Lobe

Authors: *S. JOSHI[1], G. NAVAS[2], A. MCLANE-SVOBODA[4], Z. N. ALDWORTH[5], M. A. STOPFER[6], D. SAHA[4], M. V. BAZHENOV[3];
[1]Univ. of California San Diego, San Diego, CA; [3]Dept. of Med., [2]UCSD, La Jolla, CA; [4]Biomed. Engin., Michigan State Univ., East Lansing, MI; [6]NICHD, [5]NIH-NICHD, Bethesda, MD

Abstract: Traveling waves - spatiotemporally ordered patterns of neural activity that propagate across circuits - have emerged as a fundamental computational motif across brain regions and species, yet the circuit mechanisms underlying their origins and roles in sensory coding remain poorly understood. The locust antennal lobe (AL) offers an exceptional model system to address these questions. The AL is the first central processing stage of the olfactory system, consisting of excitatory projection neurons (PNs) and inhibitory local neurons (LNs) organized into glomeruli. Odor-evoked PN activity has long been known to reflect complex spatiotemporal dynamics - rather than static population vectors - that are odor-specific and reproducible across trials

(Laurent et al., 2001). Using recurrent neural networks (RNNs) trained on in vivo locust AL data, and confirmed directly in vivo , we discovered that odor encoding is accompanied by sparse traveling waves: sequential activation of distinct PN ensembles driven by structured disinhibition from successive LN cohorts. Non-negative Matrix Factorization (NMF) of population firing rates reveals ~10 discrete temporal components across odor stimuli from 1 sec to 4 sec . This structure is circuit-determined: co-activated LN ensembles are significantly less mutually inhibitory than cross-ensemble pairs, producing the asymmetric inhibitory connectivity required for directed sequential dynamics. Disruption of LN-LN structure abolishes traveling waves, while ORN input statistics and individual cell time constants are dispensable, establishing LN-LN connectivity as the causal substrate. Traveling waves are also robust to single-neuron noise. Reanalysis of in vivo PN recordings confirmed the same sequential structure, persisting for several seconds after odor offset - consistent with a role in post-stimulus odor representation. Our findings establish the locust AL as the first system where the microcircuit substrate of a sensory traveling wave has been identified at the level of specific synaptic pathways.

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Poster

PSTR273: Olfaction: Higher-Order Circuits

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Topic: E.03. The Chemical Senses

Support: NICHD Intramural Research Program

Title: Compartmental processing within Drosophila olfactory neurons

Authors: *M. BROWN, M. A. STOPFER;
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Abstract: Sensory systems transform external stimuli into electrical signals that the brain can interpret. In many sensory systems, populations of projection neurons relay all the information of a single sensory modality from the periphery to multiple brain regions. To understand how our brains represent our sensory environment, it is critical to know how these projection neurons encode and transform information as they relay it to higher-order brain regions. The genetic, connectivity-mapping, and electrophysiological tools available in *Drosophila* help us understand how sensory information is compressed and transmitted through the brain.
In *Drosophila*, olfactory sensory neurons detecting odors in the environment synapse onto antennal lobe projection neurons (ALPNs), which are the sole carriers of information about odor identity, concentration, timing, and location to the rest of the brain. Neurons postsynaptic to the ALPNs in the mushroom body (MB) and lateral horn (LH) have their own distinct coding properties and functional roles within the olfactory circuit. Therefore, ALPNs provide an ideal

model for studying how a limited population of neurons communicates an entire sensory modality to multiple targets.
Although the MB and LH are traditionally regarded as output regions for *Drosophila* ALPNs, recent serial electron microscopy connectomes reveal that, within these regions, ALPNs also receive extensive synaptic input. We hypothesize this input allows for region-specific encoding of odor information. To test this idea, we are using precise genetic tools to evaluate connectivity and function of synaptic inputs in the MB and LH. We found that ALPNs express a broad range of neurotransmitter receptors at their terminals and receive input from LH local neurons. Additionally, we found that neurotransmitter receptor expression in the ALPNs differs between the AL and MB/LH. We hypothesize the diversity and distribution of different neurotransmitter receptors enables ALPNs to utilize different signaling speeds and regulatory mechanisms at each site of synaptic input.
We are performing *in vivo* patch clamp electrophysiology and voltage imaging of ALPNs to determine whether their odor-signaling properties vary between their origination in the AL and their eventual transmission in the MB/LH. Our work will advance our understanding of how sensory information is transformed as it moves through the nervous system.

Disclosures: M. Brown: None. **M.A. Stopfer:** None.

Poster

PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR274.01/DD12

Topic: E.05. Auditory and Vestibular Systems

Support: China STI 2030-Major Project 2021ZD0201500
NSFC T2341003

Title: Through-skull optical imaging reveals a unique dimension of natural music processing in the marmoset anterior auditory cortex

Authors: *H. WANG[1], D. CAI[2], F. XIE[2], X. SONG[1];
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Abstract: It has long been believed that music is unique to human culture. In humans, functional studies have revealed distinct areas in the superior temporal gyrus (STG) dedicated to music processing. Specifically, when comparing natural sounds to model-matched sounds that preserve only basic acoustic features, the human primary auditory cortex (AC) responds similarly to both, while the non-primary AC exhibits a strong preference for natural sounds—particularly music and songs. In contrast, non-primate models (e.g., ferrets) show no such preference in the non-primary AC. Whether the non-human primate (NHP) auditory cortex shares similarities with humans in the cortical processing of natural, music-related sounds remains unknown. To address this, we performed functional mapping in awake common marmosets (*Callithrix jacchus*) using

through-skull optical imaging to record neural responses across the entire STG, including the AC. We presented 195 natural sounds spanning 13 categories, including songs and instrumental music, alongside their respective model-matched acoustic counterparts. Analogous to human findings, the marmoset primary AC showed similar responses to both natural and model-matched sounds. However, the non-primary AC exhibited a significant preference for natural sounds, a selectivity that was consistent across 5 animals (9 hemispheres). Surprisingly, among all sound categories, natural songs elicited the largest response contrast compared to model-matched controls, predominantly localizing to the anterior AC. Furthermore, a smaller region within the anterior AC showed a significant preference for natural instrumental music. Using deep compressive neural networks, we isolated a unique dimension from the latent spaces of natural music and songs. Neural projections of this isolated dimension specifically activated the anterior marmoset AC, strongly correlating with our optical imaging findings. These results reveal that beyond basic acoustic features, a unique dimension of natural music and songs elicits specialized response patterns within the anterior NHP auditory cortex, suggesting a potential evolutionary precursor to human music processing.

Disclosures: H. Wang: None. **D. Cai:** None. **F. Xie:** None. **X. Song:** None.

Poster

PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

Support: Collaborative Research Computational Neuroscience (CRCNS) funded by the National Institute of Deafness and other Communication Disorders (NIDCD) R01DC020097-0
University of Connecticut, Institute for Brain and Cognitive Sciences (IBACS), seed grant

Title: Generalized eigendecomposition reveals coupled N100 and alpha signatures of speech-in-noise performance with a challenging signal-to-noise ratio

Authors: L. ALMOTWALY[1], T. J. HARLOW[2], J. J. CHROBAK[2], ***H. L. READ**[3];
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Abstract: The speech-evoked N100 and alpha-band oscillations have each been implicated in attentional selection in noisy auditory scenes, but how these responses jointly track listening success under highly challenging conditions remains unclear (Dimitrijevic et al., 2017, 2019). Here, twenty-seven healthy young adults attended to and recalled foreground speech digits while ignoring six naturalistic background sound types during a digit-in-noise (DIN) task at -9 dB signal-to-noise ratio (SNR). Applying generalized eigendecomposition (GED) to the EEG, the

first component reliably isolates a target-speech evoked N100 potential, explaining roughly 32% of variance on average and yielding consistent topographies within (k-fold $R^2 = 0.41$) and across participants ($R^2 = 0.43$). N100 amplitude and latency varies across background sound categories (amplitude: $F = 14.0$, $p = 2.6e-11$; latency: $F = 5.4$, $p = 1.4e-4$) and is positively correlated both across and within sound conditions. Critically, N100 amplitude tracked behavior: larger N100 response amplitudes predicted better recall across conditions ($\beta = -0.074$, $p = 9.2e-5$). Speech-event-related multitaper spectrograms estimated from the same GED component show that induced alpha power (7-13 Hz) differentiates background categories and, in late time windows, correct and incorrect recall. Generalized additive mixed models further reveal that N100 amplitude is modulated by the spectral cosine similarity of the background sound to the foreground target speech sounds, but not by its acoustical stationarity statistics (N100: F_cos = 3.893,edf = 18.822, Ref. df = 25.911, $p < 2e-16$). Behaviorally, recall varies across sound conditions and is independently predicted by the background sound acoustical statistics. Together, GED-isolated N100 and alpha responses provide coupled, behaviorally relevant readouts of speech-in-noise listening. Ongoing work examines their trial-level coupling.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.03/DD14

Topic: E.05. Auditory and Vestibular Systems

Support: NSF GRFP 23-A0-00-1010676
NIH R01DC020279

Title: Auditory feature weighting during gerbil vocalization category perception

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Abstract: Specific calls, including speech sounds, display considerable variability across vocalizers. Therefore, listeners must extract meaning by categorizing across one or more acoustic features. However, a growing literature suggests that the perception of the acoustic cues critical for aural communication displays a prolonged development. To address this issue, we developed an easily-learned behavioral paradigm that permitted us to measure vocalization categorization in both early adolescent and adult Mongolian gerbils (Meriones unguiculatus), chosen for their rich vocal repertoire and prolonged development. Animals were first trained to drink from a spout in

the presence of prototype “safe” vocalizations, and to withdraw from the spout when they heard prototype “warn” vocalizations to avoid a mild shock. After learning the procedure, we tested how animals categorized probe trials consisting of natural vocalizations that spanned the possible acoustic features of the two trained categories. Thus, in each testing session we replaced a small number of warn trials with probe trials. Adolescent (postnatal days (P) 37-55; n=14) and adult (P86-125; n=15) gerbils were tested on either ultrasonic or sonic vocalization versions of this task. A multiple linear regression (MLR) analysis was used to assess which acoustic features each animal used to perceive vocalization categories. We found that gerbils use a unique strategy for each task - the two ultrasonic vocalization categories are discriminated primarily by attending to frequency, while the two sonic vocalization categories are discriminated using a combination of multiple acoustic features, including frequency modulation and frequency (indicated by MLR betas significantly different than 0; 1-sample t-test with Bonferroni correction, $p<0.001$). On the sonic task, adolescents displayed stronger weighting on frequency than adults, while the adults placed stronger weighting on duration. Our results also demonstrated that cue weighting varies across animals, suggesting that the acoustic features used to classify vocalizations may be an individual auditory perceptual characteristic. Future work will assess how auditory cortex coding properties support vocalization perception as animals perform this task.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.04/DD15

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC016599
R01DC013073
R21DC021605

Title: Mouse inferior colliculus encodes vocalizations through acoustic feature tuning rather than categorical identity

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Abstract: The inferior colliculus (IC) is a critical auditory midbrain hub that integrates acoustic inputs across frequency, modulation, and timing. IC neurons exhibit well-characterized tuning properties to simple stimuli, yet how these feature representations combine to drive responses to complex natural sounds such as vocalizations remains unclear. Addressing this question requires methods capable of simultaneously characterizing feature tuning and vocal responses across

large neural populations at single-cell resolution.We used two-photon calcium imaging in the IC surface (dorsal cortex/lateral cortex) of awake, head-fixed mice. Neurons were systematically characterized with pure tones, AM noise, FM sweeps, and duration-varied stimuli, then tested with a set of natural mouse vocalizations presented in both forward and time-reversed configurations.IC surface responses to forward and reversed vocalizations were highly correlated, indicating that responses were largely determined by acoustic feature content rather than the categorical identity or learned meaning of vocalizations. Using a zero-parameter dot-product model—projecting each cell's frequency tuning onto the vocalization cochleagram—we accurately predicted population-level vocal response preferences, confirming that spectral template matching is the dominant coding mechanism at this stage. Beyond spectral content, we found that additional feature tuning properties, particularly duration selectivity, contributed to cell-to-cell heterogeneity in vocal responses within the IC population.These results demonstrate that acoustic feature tuning is sufficient to account for IC surface responses to vocalizations, without evidence for categorical vocal identity coding. Higher stages of the auditory hierarchy remain candidate loci for the emergence of vocalization-specific representations beyond basic feature matching.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.05/DD16

Topic: E.05. Auditory and Vestibular Systems

Support: 5R01DC014950-09

Title: Plasticity in Natural Sound Encoding following an Auditory Streaming Behavior in Ferrets

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Abstract: Tuning of auditory cortex neurons can be plastic, both rapidly and reversibly (active task engagement vs. passive listening) and over longer timescales (e.g., before vs. after learning an auditory task). These effects have been shown with pure tones, broadband noise, amplitude modulated targets. The specificity and magnitude of changes in tuning following streaming tasks utilizing natural sound targets in background noise has not been described. Recording these changes is a first step to disentangle if and how auditory cortex adjusts sensory tuning during the streaming of natural sounds. Similar to previous studies with non-natural sounds, performance of a streaming task may cause rapid shifts in neural responses that improve stimulus discriminability. Extracellular recordings were performed using Neuropixels arrays in the auditory cortex of 3 ferrets before, during, and after performance of an auditory streaming task

with natural sound targets and backgrounds. Compared to baseline, the largest magnitude in response change occurred to stimuli used in behavior after performance of the streaming task. Within the set of sounds not used in behavior, sounds most acoustically similar to the target natural sound were more likely to also change their response, compared to dissimilar sounds, suggesting shifts in natural sound tuning occur on an axis representing acoustic features, rather than only shifting responses to task exemplars. Additionally, state-induced changes (active vs passive) were much more robust than learning changes (pre-behavior vs post-behavior). Changes in natural sound responses in auditory cortex may allow for easier detection of sound comprehension or streaming when an animal is task-engaged, especially if these changes occur mainly in responses to behaviorally relevant sounds. Furthermore, these rapid changes that occur during task engagement extend for a time in the post-passive condition, which may be a substrate for learning in the auditory domain.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

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Program #/Poster #: PSTR274.06/DD17

Topic: E.05. Auditory and Vestibular Systems

Support: Israel Science Foundation grant 2453/18
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Title: Prolactin shapes auditory cortical plasticity in fathers

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Abstract: Caregiving induces plasticity in the mammalian brain to support infant survival. While the molecular and hormonal mechanisms that accompany the transition to motherhood have been studied extensively, far less is known about the biological mechanisms that shape the paternal brain. We examined whether the transition to fatherhood modifies the representation of pup ultrasonic vocalizations (USVs) in the male mouse primary auditory cortex (ACx), and what molecular mechanisms underlie this plasticity. Using longitudinal two-photon calcium imaging, we recorded the same ACx neurons in awake male mice before, during, and after fatherhood while presenting pup USVs, matched narrowband noise, and pure tones. Behaviorally, males

shifted from pup-directed aggression and self-oriented behaviors to transient parental care, accompanied by altered behavioral salience of pup vocalizations. In ACx, fatherhood induced transient changes in sound tuning and enhanced the cortical discrimination of pup USVs from acoustically matched controls. This discrimination was not only stronger but also faster, with neurons in fathers separating USVs from narrowband noise a few hundreds of milliseconds earlier as compared to before fatherhood. Slice electrophysiology revealed that fatherhood was accompanied by increased intrinsic excitability of ACx pyramidal neurons, suggesting a local cortical contribution to the enhanced coding of pup calls. Mechanistically, fathers showed elevated prolactin signaling in ACx, including increased pSTAT5 expression and upregulation of the prolactin receptor, without a concomitant increase in local prolactin levels. Acute manipulation of prolactin levels altered the temporal dynamics of USV responses and discrimination, and prolactin administration restored these temporal discrimination dynamics. Together, these results identify a fatherhood-associated form of sensory cortical plasticity in males and link prolactin signaling to experience-dependent remodeling of auditory cortical circuits that support caregiving. In the context of prior work on maternal circuitry (e.g., oxytocin-linked mechanisms), our findings highlight prolactin signaling as a candidate pathway for paternal cortical plasticity and motivate future direct comparisons across sexes.

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Poster

PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

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Program #/Poster #: PSTR274.07/DD18

Topic: F.04. Voluntary Movements

Support: NIH R01NS058487 to DEV

Title: Reduced vocal initiation variability in Rapid Eye Movement Sleep Behavior Disorder And Parkinson's Disease

Authors: *V. R. SHANKAR[1], R. VORA[1], W. KIM[1], J. J. KIM[1], R. J. MALIK[1], A. M. CHAGAS[1], T. WORTHINGTON[1], B. YACOUBI KEYHANI[1], D. E. VAILLANCOURT[1,2,3], E. A. CHRISTOU[1,3];
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Abstract: Rapid eye movement sleep behavior disorder (RBD) is a well-established prodromal condition of Parkinson's disease. Vocal deficits are common in individuals with PD and are often characterized by hypokinetic dysarthria, including reduced loudness and diminished vocal variability (monotone speech). Although limited, prior work suggests that individuals with RBD also exhibit subtle speech abnormalities (reduced prosodic variability, altered speech rhythm, and articulatory imprecision) relative to healthy controls during connected speech. However,

connected speech measures can be influenced by language, cultural background, reading demands, and stress. A simpler and more controlled approach, such as assessing vocal initiation through discrete repetition of the syllable /pa/, has not been explored. Therefore, our purpose was to determine whether vocal initiation deficits are present in RBD and whether they resemble those observed in individuals with PD. A total of 66 individuals participated in this study. Participants were age- and sex-matched into three groups: 22 healthy individuals (HC; 63.3 ± 1.7 years; 9F), 22 individuals diagnosed with RBD (63.5 ± 1.8 years; 9F), and 22 individuals diagnosed with PD (63.7 ± 1.7 years; 9F). Participants performed a vocal initiation task by vocalizing the syllable /pa/ 30 discrete times after 3 practice trials. Performance was characterized with the average and across-trial variability (coefficient of variation; CV) for the following /pa/ characteristics: peak amplitude (dB), time to peak amplitude (ms), and duration (ms). Compared with PD, HC and RBD participants exhibited a significantly ($p<0.05$) lower /pa/ peak amplitude (HC: 72.04 ± 1.24 dB, RBD: 72.20 ± 1.03 dB, PD: 77.43 ± 1.44 dB, $p<0.01$). The /pa/ time to peak (HC: 107.3 ± 5.3 ms, RBD: 108.5 ± 5.6 ms, PD: 105.8 ± 4.0 ms) and /pa/ duration (HC: 276.7 ± 14.6 ms, RBD: 279.0 ± 11.6 ms, PD: 288.6 ± 10.1 ms) was not significantly ($p>0.5$) different among the three groups. Compared with HC, RBD and PD participants exhibited significantly ($p<0.05$) reduced vocal variability as quantified with the /pa/ peak amplitude (HC: 28.9 ± 1.8%, RBD: 23.6 ± 1.1%, PD: 20.4 ± 1.1%), time to peak amplitude (HC: 25.8 ± 3.1%, RBD: 23.9 ± 1.7%, PD: 19.9 ± 1.3%), and /pa/ duration ($p<0.05$; HC: 14.9 ± 1.9%, RBD: 12.4 ± 0.9%, PD: 10.2 ± 0.6%). These findings provide novel evidence that reduced variability during discrete repetition of the syllable /pa/ is evident in RBD and PD relative to HC, suggesting that increased vocal stereotypy may serve as an early marker of PD.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

Location: WCC Halls A-C

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Program #/Poster #: PSTR274.08/DD19

Topic: E.05. Auditory and Vestibular Systems

Title: Relationship Between Chewing Sound Characteristics and Onomatopoeic Expressions Representing Food Texture

Authors: *M. TANEISHI, S. OTSUKA, S. NAKAGAWA;
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Abstract: Texture perception is a multi-modal experience influenced by both oral tactile sensations and chewing sounds. Previous studies have shown that auditory stimulation can modify perceived food texture, suggesting that pseudo-chewing sounds may enhance satisfaction with dysphagia diets. To design such sounds, the relationship between chewing sound

characteristics and perceived texture must be clarified. This study investigated the relationship between Japanese onomatopoeic expressions for food texture and the acoustic features of chewing sounds. Fourteen native Japanese-speaking adults with normal hearing participated. Eight commercially available snack foods were used. Subjective evaluations were conducted using eight Japanese onomatopoeic expressions: “saku-saku,” “zaku-zaku,” “kari-kari,” “gari-gari,” “pari-pari,” “bari-bari,” “pori-pori,” and “bori-bori.” Participants rated the correspondence between each food and each expression on a seven-point scale. Chewing sounds were recorded using a probe microphone in the ear canal and an accelerometer placed over the masseter muscle. After noise reduction and segmentation, acoustic features including spectral centroid, maximum RMS value, loudness, sharpness, and roughness were calculated. Principal component analysis revealed a clear separation between onomatopoeic expressions containing voiceless consonants (“saku-saku,” “kari-kari,” “pari-pari,” and “pori-pori”) and those containing voiced consonants (“zaku-zaku,” “gari-gari,” “bari-bari,” and “bori-bori”). To examine relationships with chewing sound characteristics, rating differences within voiced-voiceless onomatopoeic pair were correlated with acoustic features. Greater relative ratings of voiced expressions were positively correlated with maximum RMS value in both ear-canal sound pressure and vibration acceleration. Loudness and roughness showed positive correlations with voiced-expression ratings, whereas spectral centroid exhibited different trends between ear-canal sound pressure and vibration acceleration. These results suggest that chewing sounds with greater instantaneous energy tend to be described using voiced onomatopoeic expressions. The findings indicate that acoustic properties of chewing sounds are reflected in texture-related onomatopoeic expressions and may support the development of realistic pseudo-chewing sounds to enhance texture perception in dysphagia diets.

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Poster

PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

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Topic: E.05. Auditory and Vestibular Systems

Support: Burroughs Wellcome Fund PDEP
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US NSF IOS-1655825

Title: Sex differences in the development of tuning for vocal acoustics in the auditory cortex

Authors: *K. SHADRON[1], S. M. N. WOOLLEY[2];
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Abstract: During development, the brain uses sensory input to shape the organization of neural circuits underlying learned behavior. There is evidence that inherited traits can prime the brain to

encode behaviorally-relevant information during development. How genetic background influences the early learning process and shapes future behavior is unknown. Here, we studied songbirds to identify mechanisms by which sensory biases in auditory processing emerge from genetic background and experience. Songbirds share with humans the rare trait of vocal learning. During a developmental critical period, juvenile males memorize their adult tutors' songs and use auditory feedback to practice and perfect their own song. Male song conveys information about the species and individual identity to females during mate choice. Work across species shows that the juveniles of both sexes prefer to hear conspecific song over heterospecific song, even without prior song exposure. This suggests that preference for conspecific song of both sexes has a genetic component. If raised by heterospecific tutors, juveniles will learn heterospecific song acoustics, indicating an interplay between genetic background and early-life experience in song development. In tutored adults, auditory cortical neurons are tuned to the acoustics of learned song. However, how this song selectivity develops in the auditory cortex is not known. Here, we examined and compared neuronal tuning for song acoustics in tutored and untutored juveniles of both sexes. We performed electrophysiological recordings of the auditory cortex of zebra finch (*Taeniopygia guttata castanotis*) and Bengalese finch (*Lonchura striata* var. *domestica*) juveniles of both sexes. Recordings were performed in tutored and untutored individuals. The tuning property that accurately predicts neuronal song responses is tuning for spectrotemporal modulations, not tone responses. As such, tuning to song acoustics was assessed using responses to spectrotemporal modulations. We compared neural selectivity for spectrotemporal modulations in zebra and Bengalese finches, and mapped tuning onto modulations in song, to identify genetic versus experience-dependent tuning. Preliminary results indicate that neural tuning to the spectral modulations present in conspecific song is developed in male juveniles before song exposure, and tuning to spectrotemporal modulations (e.g. frequency modulated sweeps) develops later. Non-tutored females do not show tuning to spectral modulations at this developmental timepoint. These results show that the auditory tuning in male and female songbirds have different developmental trajectories.

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Poster

PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

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Program #/Poster #: PSTR274.10/DD21

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R15DC020847
PSC-CUNY 68680-00 56

Title: Epigenetic regulation of auditory memory-related gene expression in the aging zebra finch brain

Authors: A. C. XANDERS[1], S. ELNAWAWI[1], D. S. VICARIO[2], M. L. PHAN[2], *C. L. PYTTE[1];
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Abstract: Age-related decline in auditory memory for learned vocalizations contributes to impairments in speech processing, social communication, and cognitive health, yet the neural mechanisms underlying auditory memory formation in aging brains remain poorly understood. Songbirds provide a unique translational model for studying auditory memories for learned vocalizations because, like humans, they form long-term memories of vocal communication signals. Histone deacetylase 3 (HDAC3) is a negative regulator of memory processes, and inhibition of HDAC3 enhances memory formation, persistence, and specificity. However, the molecular effects of HDAC3 inhibition during the formation of auditory memories for natural vocalizations are not yet known. Here we examined how HDAC3 inhibition with RGFP966 alters gene expression associated with age-related auditory memory decline in the zebra finch auditory forebrain, caudomedial nidopallium (NCM). Middle-aged (n=12 males, 14 females) and old (n=16 males, 16 females) zebra finches received playback of 8 novel conspecific songs in sets of 20 repetitions per stimulus. Twenty presentations are sub-threshold for long-term memory formation in controls but sufficient to induce memory following RGFP966 treatment (Phan et al., 2017). Birds received RGFP966 or vehicle immediately following playback and were sacrificed 30 min later. RNA-sequencing of NCM identified robust age-related transcriptional changes in control birds. Aging was associated with increased expression of genes related to glial signaling (GJC2), cytoskeletal remodeling (ARHGEF12), and inflammaging (UBASH3B), and decreased expression of genes associated with neurotrophin signaling (DOK5), autophagy/proteostasis (SCOC), and metabolic and oxidative stress regulation (ALDH9A1, ADI1). Compared with control birds, RGFP966 treatment induced increased expression of genes associated with synaptic plasticity and memory-related signaling including SMOX, DUSP7, TOB1, SYPL1, and ZFP36L1. These genes are implicated in NMDA receptor modulation, MAPK/ERK signaling central to memory consolidation, activity-dependent transcription, vesicle trafficking, and progenitor-cell regulation. Collectively, these findings suggest HDAC3 inhibition with RGFP966 may promote plasticity in the higher order auditory region NCM in the aging brain.

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Topic: E.05. Auditory and Vestibular Systems

Support: NSF IOS-1942480
NIH 1F31DC023420-01

Title: Internal prediction of zebra finch song syntax

Authors: *B. LE[1], C. MELIZA[2];
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Abstract: Learned vocal communication can alter how the brain responds to acoustic stimuli. When presented with noisy or incomplete speech, the brain compensates for the missing input by making predictions based on its internal model of what the speech pattern should be, drawing on contextual information and prior experience. In the auditory restoration illusion, internal neural dynamics are strong enough to override pure noise input with the illusory perception of non-existent speech phonemes. Male zebra finches similarly learn to vocalize their songs, each an acoustically-rich but stereotyped syllable sequence, from a tutor. Syllable categories and transition probabilities are highly consistent across conspecific individuals and populations, suggesting a universal syntactic structure to the songs. Our previous work demonstrated that neurons in the zebra finch auditory pallium responded to conspecific songs with noise-occluded syllables as though the missing syllables were present, even when birds were under anesthesia and had no prior exposure to the singer, but not when the syllables were embedded in unnatural syntax. Though these results suggest that the finch pallium has an internal predictive model of its species' songs syntax, it is not known whether or not this model depends on experience. Here, we describe the neural dynamics during the illusion in adult finches that were reared in acoustically impoverished environments, wherein birds were exposed to either limited syntactic information or none at all during early development. Further, we show how the context-dependent neural prediction of missing song syllables correlates to the perceptual illusion by engaging birds in a gap-detection task. Our results suggest that the zebra finch is able to fill in missing syllables even without exposure to conspecific vocalizations.

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PSTR274: Auditory Processing of Vocalizations, Natural Sounds, and Speech

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Topic: F.04. Voluntary Movements

Support: Eagles Pilot Grant/Norman Fixel Institute for Neurological Diseases

Title: Neurophonics: Reliability of a Tablet-Based Acoustic Voice Assessment for Quantifying Speech Production

Authors: *W. KIM[1], R. J. VORA[1], V. R. SHANKAR[1], R. J. MALIK[1], A. M. CHAGAS[1], T. W. WORTHINGTON[1], J. J. KIM[1], B. YACOUBI KEYHANI[1], E. A. CHRISTOU[1,2];
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Abstract: We developed a tablet-based voice assessment application, Neurophonics, to provide an efficient and accessible method for quantifying acoustic characteristics of speech production. The purpose of this study was to determine the test-retest and intra-rater reliability of acoustic measures obtained with Neurophonics. Intra-rater reliability was examined across three raters in 46 participants (22±3.8, 32 F), and test-retest reliability was assessed in 12 participants (24±5.3, 1 F) who completed three testing sessions separated by two-day intervals. Participants performed three sustained vowel (/a/) phonations and 30 repetitions of a vocal initiation task involving discrete production of the syllable /pa/ at normal amplitude. For the sustained vowel task, we quantified the fundamental frequency (F0), F0 variability (F0 range), and loudness during the stable portion of the acoustic signal (2-6 s). For the vocal initiation task, we quantified peak amplitude (PeakAmp) and time to peak amplitude (TPAmp) across the 30 repetitions. During the sustained vowel task, F0 demonstrated excellent test-retest reliability (ICC = 0.91, 95% CI [0.76, 0.97]) and excellent intra-rater reliability across all raters (ICC = 0.91-1.00). Loudness exhibited good test-retest reliability (ICC = 0.83, 95% CI [0.58, 0.95]) and good-to-excellent intra-rater reliability (ICC = 0.89-0.99). F0 range demonstrated moderate test-retest reliability (ICC = 0.57, 95% CI [-0.21, 0.87]) and moderate-to-good intra-rater reliability (ICC = 0.54-0.83).For the vocal initiation task, PeakAmp showed good test-retest reliability (ICC = 0.79, 95% CI [0.45, 0.94]) and excellent intra-rater reliability (ICC = 0.92-0.99). TPAmp demonstrated good-to-excellent test-retest reliability (ICC = 0.88, 95% CI [0.69, 0.96]) and excellent intra-rater reliability (ICC = 0.82-0.97). Together, these findings demonstrate that Neurophonics provides reliable acoustic measures of sustained phonation and vocal initiation, supporting its potential as an accessible tool for objective voice assessment and longitudinal monitoring.

Disclosures: W. Kim: None. **R.J. Vora:** None. **V.R. Shankar:** None. **R.J. Malik:** None. **A.M. Chagas:** None. **T.W. Worthington:** None. **J.J. Kim:** None. **B. Yacoubi Keyhani:** None. **E.A. Christou:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.01/DD24

Topic: E.05. Auditory and Vestibular Systems

Support: NIH/NIDCD T32 DC000046
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Title: Dorsal auditory cortex preferentially encodes task outcome during active listening

Authors: *M. MCCOLLUM, M. L. CARAS;
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Abstract: Sensory systems dynamically adjust neural processing according to behavioral demands and environmental context. We previously demonstrated that the orbitofrontal cortex

(OFC) is highly sensitive to context, and its activity is required for task-dependent plasticity in the primary auditory cortex (A1) and for the detection of behaviorally-relevant sounds. Although OFC projects directly to A1, its densest auditory cortical projection targets the dorsal auditory cortex (AuD), which is reciprocally connected with both OFC and A1. This connectivity places the AuD in a unique position to mediate interactions between OFC and A1, and raises the possibility that it may play an important role in context-dependent auditory processing. However, how behavioral context shapes AuD activity remains poorly understood. To address this question, we made chronic extracellular recordings from AuD in Mongolian gerbils during the performance of an amplitude modulation (AM) detection task and during passive presentations of the same AM stimuli. We found that AuD is strongly modulated by behavioral context, exhibiting a robust increase in activity during task performance relative to passive sound exposure. During task performance, neural responses were strongly influenced by trial outcome, and only weakly modulated by AM depth. Notably, these response dynamics closely resembled those previously observed in the OFC. These findings indicate that AuD preferentially represents task information rather than acoustic stimulus features during active listening. We propose that AuD serves as an auditory cortical conduit for outcome-related signals that may influence processing in A1 and other downstream auditory regions.

Disclosures: M. McCollum: None. **M.L. Caras:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.02/DD25

Topic: E.05. Auditory and Vestibular Systems

Title: Noise-induced hearing loss disrupts auditory cortex to parietal cortex transformations during sound-guided decision-making

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Abstract: Noise-induced hearing loss (NIHL) is a leading cause of sensory impairment resulting from exposure to loud noise and is accompanied by deficits in speech comprehension and cognitive function. However, the neural mechanisms linking NIHL to cognitive dysfunction remain unclear. Here, we tested whether NIHL disrupts the transformation of auditory sensory representations into decision variables across cortical networks. Gerbils were trained on a single-interval alternative forced-choice task requiring discrimination of slow versus fast presentation rates of amplitude-modulated (AM) broadband noise. Extracellular activity was recorded from neurons in auditory cortex (AC) and parietal cortex (PC) during task engagement and passive listening under normal-hearing conditions and after permanent NIHL induced by controlled broadband noise exposure. Post-NIHL stimuli were presented at sensation levels matched to pre-NIHL conditions to compensate for elevated auditory thresholds and to isolate central

consequences of hearing loss. NIHL impaired decision-making task performance. In AC, neural populations continued to encode AM rate and stimulus category after NIHL, but categorical decoding was degraded. Post-NIHL AC neurometric performance remained better than behavioral performance, suggesting that auditory cortical populations retained sensory information that was not efficiently utilized for decision-making. In contrast, PC activity more closely reflected behavioral performance. Under normal-hearing conditions, PC population decoding distinguished slow from fast AM rates and matched psychometric performance. After NIHL, PC decoding was severely degraded and aligned with impaired decision-making behavior. These findings indicate that NIHL does not simply abolish cortical sensory representations, but instead, hearing loss disrupts the downstream transformation of available auditory information into decision-related representations. This sensory-to-cognitive disruption provides a circuit-level mechanism by which peripheral hearing loss may contribute to broader cognitive dysfunction.

Disclosures: K. Zemlianova: None. **J. Yao:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.03/DD26

Topic: E.05. Auditory and Vestibular Systems

Title: An Image-Based Detection Approach to Identify Tinnitus-Associated Behavioral Patterns in Mice

Authors: S. SHAPIRO[1], E. DAY[2], A. ZANG[3], ***J. BAO**[3], J. PINKL[3];
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Abstract: The lack of reliable preclinical tinnitus detection methods remains a major barrier to basic and translational tinnitus research. Previously, our laboratory developed and validated a behavioral assay for tinnitus detection known as sound-based avoidance detection (SBAD). Although SBAD effectively identifies tinnitus in animal models, its relationship to tinnitus associated psychological changes remains unclear. Here, we developed an image-based tinnitus detection (IBTD) approach using automated video tracking. Mice with and without tinnitus, identified using SBAD, were monitored with EthoVision XT to quantify spontaneous activity. Analyses were performed in two tinnitus models: a novel chemogenetic *transient tinnitus* (TT) model and a well-established *chronic* noise-induced *tinnitus* (CT) model. In the TT model, excitatory designer receptors exclusively activated by designer drugs (DREADDs) were targeted to glutamatergic neurons in the central nucleus of the inferior colliculus of ten adult C57BL/6 mice. Intraperitoneal administration of clozapine-N-oxide (CNO) transiently activated transfected neurons. In the CT model, 40 C57BL/6 mice were exposed to broadband noise (8-16 kHz, 110 dB SPL) for 4 h. Comparisons of pre- and post-induction SBAD measures identified

tinnitus-associated behaviors in 5 TT mice and 6 CT mice. In the TT model, tinnitus induction produced significant within-subject changes (adjusted Benjamini-Hochberg FDR procedure with q = 0.05) in 15 video-derived activity features spanning locomotor, postural, and movement-pattern behaviors. Although not all features generalized across models, six behavioral measures were consistently altered in both TT and CT mice, suggesting shared behavioral signatures of transient and chronic tinnitus. These findings support the feasibility of the IBTD framework as a complementary tool to the SBAD method. In addition, this new IBTD method may identify key features often associated with tinnitus such as anxiety. Thus, integrating passive behavioral monitoring with conditioned behavior may improve preclinical phenotyping of tinnitus and evaluation of potential therapeutic interventions in mice.

Disclosures: S. Shapiro: None. **E. Day:** None. **A. Zang:** None. **J. Bao:** None. **J. Pinkl:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

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Program #/Poster #: PSTR275.04/DD27

Topic: E.05. Auditory and Vestibular Systems

Support: NIH RO1DC017785 (POK)

Title: Distributed encoding of behavioral variables in auditory cortex shows structured laminar and subregional organization

Authors: *M. WANG[1], P. O. KANOLD[2];
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Abstract: Sensory cortices comprise multiple subareas and layers, yet how areas jointly encode both sensory and behavior-related information and their laminar distinctions is unclear. Here, we used two-photon calcium imaging to record the activity of ~200000 neurons from >300 behavioral sessions across layers (2-5) and subregions of the auditory cortex (ACtx) in mice performing a two-alternative forced-choice auditory task. We examined excitatory neurons labeled by Thy1 (Thy1-GCaMP6s; B6.CAST-Cdh23Ahl+/Kjn) or Cux2 drivers (Cux2tm3.1(cre/ERT2)Mull; B6.CAST-Cdh23Ahl+/Kjn; Ai162(TIT2L-GC6s-ICL-tTA2)-D), as well as projection-defined corticostriatal neurons. We found that neurons encoding sensory, motor, or outcome variables were broadly distributed and that their mixed-encoding properties reflected the learned task rules. The timing of sensory, motor, and outcome information varied across information types, subregions, and layers, suggesting a distinction in the laminar processing hierarchy for different behavioral variables within primary or higher-order ACtx subregions. Further analysis of the population activity suggests a more parallel, antagonistic, or homogenous circuitry involved in sensory, motor, or outcome encoding, respectively. The response properties of Cux2+ neurons resembled those in the Thy1+ population, suggesting a relatively conserved circuitry across these excitatory neuron populations. TS-projecting neurons

were more mixed-selective and showed faster sensory and motor encoding, suggesting their specialized roles in sensorimotor integration. Together, these findings support a distributed yet structured organization of behavioral encoding in ACtx, shaped by laminar-, subregional-, and cell-type-specific circuitry that reflects and adapts to learned behavioral tasks.

Disclosures: M. Wang: None. **P.O. Kanold:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.05/DD28

Topic: E.05. Auditory and Vestibular Systems

Title: Cortical and peripheral interactions in auditory inhibion of return

Authors: *M. MATSUGE, S. OTSUKA, S. NAKAGAWA;
Chiba Univ., Chiba, Japan

Abstract: When exogenous attention to either ear is induced by a cue, reaction time (RT) to targets presented at the cued location is initially facilitated, whereas this effect reverses after several hundred milliseconds, a phenomenon known as inhibition of return (IOR). Our previous findings revealed that otoacoustic emissions (OAEs), reflecting outer hair cell (OHC) motility, were associated with behavioral performance during IOR but not exogenous attention. This implies that the central nervous system dynamically recalibrates peripheral sensory receptors based on attentional dynamics. To determine whether distinct neural substrates drive this regulation, we examined the relationship between OAEs and event-related potentials (ERPs). 13 normal-hearing individuals (8 men, 5 women; aged 21-25) participated in this study. The stimuli consisted of a 500-Hz cue tone followed by a two-tone complex target that evoked distortion-product OAEs (DPOAEs). The cue and target were presented either ipsilaterally (cued) or contralaterally (uncued). Stimulus onset asynchrony (SOA) was set to 0.125 and 0.725 s to capture exogenous attention and IOR, respectively. To evaluate attention-induced modulations, differences between attended and unattended conditions were calculated for both ERP waveforms (ΔERP) and DPOAE levels (ΔDPOAE). ΔERP showed a sustained positive shift for 0.6 s after target onset in both SOAs. Correlation analyses between ΔDPOAE and point-by-point ΔERP revealed significant negative correlations over parietal electrodes in both SOAs, indicating that larger positive ERP shifts were associated with greater DPOAE reductions in the attended ear. In the short SOA condition, these correlations persisted across a broad latency range, suggesting involvement of extensive cortico-cortical and corticofugal networks. In contrast, correlations in the long SOA condition were restricted to early post-target latencies, suggesting a more localized contribution that presumably originates within or around the auditory cortex. Although previous fMRI studies have shown that exogenous attention and IOR recruit overlapping frontoparietal regions, our findings reveal a temporal reorganization of corticofugal networks. During exogenous attention, cortical-peripheral modulation engages higher-order

cortical circuits involved in conscious spatial orienting. During IOR, however, modulation bypasses these circuits and is driven by cue-defined spatial coordinates via auditory cortical feedback. This reorganization may support rapid peripheral modulation by minimizing higher-order processing demands.

Disclosures: M. Matsuge: None. **S. Otsuka:** None. **S. Nakagawa:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

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Program #/Poster #: PSTR275.06/DD29

Topic: E.05. Auditory and Vestibular Systems

Support: The Hilary and Galen Weston Foundation

Title: Syncopation in musical rhythms drives neural and behavioral variability during listening and sensorimotor synchronization

Authors: *R. FAR[1,4,5], E. FLATEN[6], K. KIM[1], L. FRANCO VERGARA[1,4], L. MILOSEVIC[1,4], L. MELLONI[7], N. JACOBY[8], T. A. VALIANTE[1,4,2,3];
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Abstract: Humans naturally tend to move in time with rhythmic music. Syncopation (a measure of rhythmic complexity characterized by deviations from expected metrical structure) is a musical property known to influence the pleasurable urge to move to music. However, the precise neural mechanisms underlying these affective and auditory-motor responses to music are not well understood. Here, we employed high-resolution human intracranial electroencephalography (iEEG) together with a behavioral task to examine how syncopation modulates neural encoding and motor synchronization to musical rhythms. We collected iEEG recordings from 15 adults with medication-refractory epilepsy implanted with depth electrodes for seizure localization. Participants listened and tapped along to drum patterns with uniform beat frequency and balanced acoustic features, but with varying Syncopation Index (SI), where higher SI denotes greater rhythmic complexity. To quantify neural tracking of the musical beat, we extracted instantaneous phase angle time series from iEEG local field potentials (LFPs) at the beat frequency (1.95 Hz), then computed phase locking values between the LFPs and each stimulus. Statistical significance was assessed using permutation testing. 308 electrode contacts from 15 participants were analyzed. 31 electrodes from both auditory and nonauditory brain regions demonstrated significantly greater phase locking to the beat during low SI compared to high SI stimuli. Neural phase locking patterns displayed remarkable similarity to motor

behavioral data from the same participants, where low SI stimuli elicited greater tapping consistency. Interestingly, these behavioral differences did not depend on conscious perceptions of stimulus complexity, assessed via participants' subjective ratings. While auditory cortex LFPs showed phase locking in all conditions, thalamic LFPs only did so during active tapping but not passive listening, highlighting the distinct and overlapping neural circuits underlying auditory-motor coupling behavior. Altogether, we show that syncopation in musical rhythms modulates low-frequency neural oscillations across a wide anatomic distribution, in a way that closely mirrors behavioral oscillations. Future work will integrate this dataset with basal ganglia microelectrode recordings obtained from individuals undergoing deep brain stimulation for Parkinson's disease, to further delineate the interplay between auditory and motor systems in generating music-induced movement. Improved understanding of this phenomenon may lead to more effective applications of music as a form of non-invasive neuromodulation.

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Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

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Program #/Poster #: PSTR275.07/DD30

Topic: E.05. Auditory and Vestibular Systems

Title: Measurement of cortical and brainstem activity involved in perception of consonance: Validation of correlation with psychological measures

Authors: *T. TOYA[1], S. OTSUKA[2,3], S. NAKAGAWA[2,3,4];
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Abstract: It is well known that the perceived consonance in musical chords increases when their constituent frequencies form simple integer ratios and decreases as these ratios become more complex. In chords with complex frequency ratios, interference between closely spaced frequency components gives rise to beat frequencies (Δf), which manifest as amplitude modulation in the time waveform. This observation suggests that perceptual mechanisms that are sensitive to Δf may contribute to the perception of consonance and dissonance. However, despite extensive psychophysical evidence, the neural basis of consonance perception remains unclear. Several previous studies have reported significant differences in brain function associated with individual differences in auditory ability. With respect to consonance perception, some studies have suggested that individual differences in harmonic discrimination are reflected in both cortical and brainstem activity. Nevertheless, no studies have yet simultaneously measured and directly compared cortical and brainstem responses related to consonance perception; thus, the respective roles of these regions remain unclear. In the present study, we measured

psychophysical responses (paired comparison), cortical responses (mismatch negativity: MMN), and brainstem responses (frequency-following response: FFR) to six musical triads with different degrees of consonance in normal-hearing participants. Consonance was manipulated by altering the ratios of constituent frequencies. For MMN measurements, we employed an oddball paradigm in which dissonant chords served as deviants and major chords served as standards. These stimuli were designed so that neither the standard nor the deviant chords contained physically deviant frequency components that could elicit a low-level MMN. In addition, the standard chords were transposed across five keys to ensure that the elicited MMN reflected differences in consonance perception rather than simple acoustic deviance. For FFR measurements, neural pitch salience, an index of the clarity of pitch encoding for each chord stimulus, was derived from the recorded responses. MMN amplitude showed a moderate negative correlation with psychological scale values ($r = -0.44$), whereas FFR-derived pitch salience exhibited a strong positive correlation ($r = 0.87$). These findings suggest that, although both cortical and brainstem processing contribute to the perception of consonance, brainstem activity may play a more prominent role.

Disclosures: T. Toya: None. **S. Otsuka:** None. **S. Nakagawa:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

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Topic: E.05. Auditory and Vestibular Systems

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Title: Neural Representations of Action-Effect Prediction and Prediction Error in Naturalistic Coupling

Authors: *X. WANG, L. CAO;
Zhejiang Univ., Hangzhou, China

Abstract: Actions are accompanied by sensory feedback (i.e., action-effects), which is typically predictable in natural contexts. Prediction errors arise when actual feedback violates prior expectations. Most previous studies on action-effect prediction and prediction error have largely relied on arbitrary action-effect associations, leaving it unclear how the brain represents prediction and prediction error when action-effect relations are naturally grounded. To address this, the present study investigated neural representations of action-effect prediction and prediction error using natural mappings between keypress force and auditory intensity. In two EEG experiments, participants voluntarily produced a strong or weak keypress in each trial, followed by loud or soft auditory feedback with a 100 ms delay. Strong and weak keypresses

were naturally associated with loud and soft sounds in Experiment 1, with occasional mismatched feedback inducing prediction errors. Experiment 2 reversed the mapping as a control. Results showed that robust N2 and P3 components were elicited in prediction error trials under both natural and reversed mappings. Importantly, dissociable neural responses were found for loud and soft violations: unexpected loud feedback led to enhanced N2 activity, whereas unexpected soft feedback led to enhanced P3 activity. In addition, stronger keypresses induced a larger pre-action readiness potential (RP), yet there was no evidence that predictable action effects reliably modulated the RP. Our findings reveal how auditory feedback violations shape the temporal dynamics and depth of prediction error processing, providing ecologically grounded evidence for predictive processing in action-effect coupling. These findings also support the extended auditory event representation model and are compatible the theory of event coding.

Disclosures: X. Wang: None. **L. Cao:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC022778
NIH Grant EY030669

Title: Activity in primate superior colliculus during a reward-biased auditory spatial discrimination task

Authors: *C. CONROY[1], Y. E. COHEN[2], R. M. MCPEEK[1];
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Abstract: Previous work has shown that the primate superior colliculus (SC) is involved in the discrimination of visual stimuli. For example, when visual discrimination decisions are reported using eye movements, SC activity can be related to the response biases (decision criteria) that bear on decision formation. Inactivation or microstimulation of the SC, moreover, can introduce response biases into visual discrimination tasks. While this previous work has focused on visual discrimination, the primate SC also receives auditory input. Little is known, however, about the role of the SC in the discrimination of auditory stimuli or if, in auditory tasks, SC activity is related to response biases. In this study, therefore, we examined SC activity—spiking and local field potentials (LFPs)—during an auditory spatial discrimination task involving manipulations of response bias. On each trial, a rhesus monkey fixated a central point and two visual-saccade targets were presented: one in the response field (RF) of the SC recording site, and the other in the opposite hemifield. An auditory noise burst was then presented in either the left or right hemifield, and, following a brief delay period, the monkey was tasked with reporting the

hemifield of the noise by making a saccade to the corresponding visual-saccade target (i.e., the left target for noises presented to the left and the right target for noises presented to the right). Response bias was manipulated by presenting blocks of trials with an asymmetry in the relative rewards associated with correct-left versus correct-right decisions. In a preliminary dataset from one monkey, in most sites, there was an increase in spiking activity and greater negativity in the LFPs before and during the presentation of the noise burst when the monkey was biased to report that the noise was in the same hemifield as the RF. At the same time, the peak-to-peak magnitude of the auditory stimulus-evoked LFP transient appeared largely unaffected by response bias in most sites. The stimulus-evoked activity was followed by a flip in the order of the LFPs such that, when the monkey was biased to report that the noise was in the same hemifield as the RF, LFPs were more positive in the delay period preceding saccade onset. Overall, the preliminary data point towards a relationship between SC activity and response bias in auditory tasks, as well as a role for the primate SC in nonvisual perceptual decisions.

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Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

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Program #/Poster #: PSTR275.10/EE2

Topic: E.05. Auditory and Vestibular Systems

Support: NIH RO1DC017785
NIH F31 DC022515

Title: Effect of stimulation of target frequency-responsive auditory cortical cells on discrimination task performance

Authors: *J. I. DAHER, P. O. KANOLD;
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Abstract: For many animals, auditory discrimination is critical for engagement with one's environment, with distinguishing between familiar sounds and categorizing unfamiliar sounds being important skills for survival. Despite the importance of auditory stimuli in our daily lives, the role of the auditory cortex in this task has yet to be fully understood. Manipulations to the auditory cortex in behaving animals have been reported to have a wide variety of effects on task performance, with results varying depending on task design, complexity of the stimuli used, and the nature of the manipulation. We investigated the role of auditory cortical cells in mice performing a pure-tone discrimination task, using two-photon imaging and holographic optogenetic stimulation. Expert animals co-expressing GCaMP8s and the opsin rsChRmine in cortical neurons were imaged during performance of a pure-tone wheel-based two-alternative forced choice (2AFC) discrimination task, while cells tuned to either a given target tone ("matched" group) or the opposing tone ("opposite" group), as identified from a passive tuning

session preceding the task, were optogenetically stimulated. Preliminary results suggest that stimulation of these groups is sufficient to elicit an effect on task performance.

Disclosures: J.I. Daher: None. **P.O. Kanold:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.11/EE3

Topic: E.05. Auditory and Vestibular Systems

Title: Greater Listening Engagement during audiovisual than auditory-only listening, as reflected by interpersonal synchronization

Authors: *L. LAMBRECHTS, B. ACCOU, J. VANTHORNHOUT, B. BOETS, T. FRANCART;
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Abstract: Listening engagement has been recognized as a crucial factor in predicting successful listening experiences. This concept refers to the immersive experience individuals can have while listening and is assumed to positively impact memory retention and overall well-being. However, there is still uncertainty about which factors affect listening engagement. Theoretical frameworks indicate that specific characteristics of speech sounds, including the topic and form of presentation (auditory only vs audiovisual), can influence this engagement. Recent literature further suggests that listening engagement tends to be higher with audiovisual materials than with auditory-only presentations. Despite these findings, previous studies did not adequately account for participants' level of listening engagement, complicating the interpretation of the results. We conducted an experiment with 30 participants to examine the impact of different stimulus modalities on listening engagement. We measured interpersonal synchronization of brain and body responses, reflecting the extent to which these responses fluctuate together across individuals while they listen to or view podcasts. Interpersonal synchronization has become increasingly recognized in continuous speech experiments as indicative of a listener's state and, in particular, of listening engagement. Our study utilized a 2x2 experimental design, featuring both engaging (interesting) and non-engaging (boring) stimuli alongside auditory-only and audiovisual presentations. We measured brain activity (EEG), heart rate, and electrodermal activity to assess interpersonal synchronization in these conditions. Additionally, subjective ratings of listening engagement served as a ground truth for our stimulus manipulations. The results showed that interpersonal synchronization was significantly greater for engaging stimuli compared to non-engaging ones. Moreover, the audiovisual format increased listening engagement, as reflected by interpersonal synchronization, indicating that multimodal input can effectively facilitate engagement with speech. These findings suggest that both topic interest and presentation format shape how we listen to and perceive speech. They may inform the design of

future experimental protocols and improve our understanding of effective everyday information transfer.

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Poster

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Program #/Poster #: PSTR275.12/EE4

Topic: E.05. Auditory and Vestibular Systems

Title: Hierarchical representations of song acoustics and lyrics in auditory cortex

Authors: *R. CASSANO-COLEMAN[1], S. V. NORMAN-HAIGNERE[2], C. R. IORDAN[3], E. A. PIAZZA[1];
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Abstract: The brain processes complex stimuli hierarchically: as information travels from primary sensory cortices to secondary areas and beyond, neural representations become more abstract and more categorical. In audition, hierarchical neural processing has been primarily studied for speech and isolated sounds (Chang et al., 2010), but it remains unclear how auditory cortex represents different aspects of song during naturalistic music listening. Here, we sought to address this question by comparing neural processing between pairs of natural songs that share lyrics but not low-level acoustics (e.g., originals and cover versions) versus pairs of songs that share low-level acoustics but not lyrics (e.g., originals and lyric-swapped versions of the same songs). Eleven subjects (ages 18 to 22, 7 female) listened to 20 songs across all four conditions (original, cover, lyric-swapped original, lyric-swapped cover) in the fMRI scanner. We then computed the inter-subject pattern correlation (ISPC) within and across conditions for all stimuli (averaged in time) in primary (A1) and secondary auditory cortex (anterior and posterior superior temporal gyrus [aSTG, pSTG]) in MNI152 space. We found reliable patterns of neural activity across subjects within and across all four conditions in A1 and STG. Furthermore, in A1, we found that neural patterns were more highly correlated between conditions where acoustic information was matched versus not matched (marginally significant, Wilcoxon rank-sum test, $p = .065$), but there was no difference in pattern correlation for matched lyrics versus non-matched lyrics ($p = .88$). This suggests that A1 primarily encodes low-level acoustic information in songs, consistent with prior work with other kinds of stimuli. We found the opposite effect in both aSTG and pSTG: neural patterns were more highly correlated between pairs of conditions where lyrics were matched versus not matched (aSTG: $p = .083$, pSTG: $p = .010$), but there was no difference between matched versus non-matched acoustics (aSTG: $p = .96$, pSTG: $p = .96$). This suggests that secondary auditory areas are primarily extracting and representing meaningful higher-level song information. These preliminary results are a step towards a more complete

understanding of how the human brain hierarchically processes and represents music and song in everyday listening.

Disclosures: R. Cassano-Coleman: None. **S.V. Norman-Haignere:** None. **C.R. Iordan:** None. **E.A. Piazza:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.13/EE5

Topic: E.05. Auditory and Vestibular Systems

Support: CMU Rales Fellowship

Title: From sound to action: cell-type-specific corticostriatal coding during auditory learning

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Abstract: For all mammals, survival depends on learning which environmental features predict reward and using that information to guide behavior, a process supported by plasticity in projections from sensory cortex to the dorsal striatum. In the auditory system, these projections arise from two classes of layer 5 (L5) pyramidal neurons: intratelencephalic (IT) neurons, which collateralize to other cortical areas and may form contextual representations of sound, and extratelencephalic (ET) neurons, which collateralize to subcortical structures involved in behavioral execution. Both populations project to the caudal tail of the dorsal striatum (TS), which fine-tunes learned sound-action associations late in learning, but only IT neurons project to the rostral dorsal striatum (RS), which is canonically involved in initially forming sound-reward and sound-action associations. Here, we examined how cell-type-specific activity in the auditory cortex supports auditory-guided learning. We trained mice on a head-fixed associative learning task in which one of two sinusoidally amplitude-modulated (sAM) noise bursts predicted a water reward after a short (0.5 s) delay. We simultaneously used body and orofacial cameras to track all movements across learning. While mice learned to discriminate between the two stimuli, we recorded activity from either L5 IT or L5 ET neurons using two-photon calcium imaging. Linear population decoding (n=5 mice) shows that both cell types robustly encode spontaneous and sound-evoked behaviors. In early learning, L5 IT neurons encode sound-evoked movements more strongly than L5 ET neurons; this pattern reverses in middle and late learning, when L5 ET neurons encode them more strongly. These dynamics lead us to hypothesize that L5 IT->RS projections facilitate early sound-reward associations, whereas L5 ET->TS projections contribute to the execution of learned behaviors later in learning. To test this, in ongoing experiments we use retrograde labeling to resolve how each of three corticostriatal pathways (L5

IT->RS, L5 IT->TS, and L5 ET->TS) represents associations among sounds, rewards, and actions across learning.

Disclosures: C.B. Michel: None. **N.A. Schneider:** None. **R.S. Williamson:** None.

Poster

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Program #/Poster #: PSTR275.14/EE6

Topic: E.05. Auditory and Vestibular Systems

Support: E.H. Solomon Center for Neurodevelopmental Research

Title: Early acoustic intervention further differentiates neural patterns of auditory perception

Authors: *L. A. MILOVIC, R. D. MILL, M. W. COLE, A. A. BENASICH;
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Abstract: Rapid auditory processing (RAP), the ability to detect, discriminate, and resolve temporally modulated acoustic input, is essential to language acquisition. Using human infant electroencephalography (EEG) measures, prior research has identified neural biomarkers of RAP on the scalp-level. Our current advances use finite-element head modeling, beamformer source-reconstruction, and infant-appropriate anatomical templates, to identify neural underpinnings of the cortical maturation and temporal efficiency previously observed. We obtained multivariate spatiotemporal similarity indices from the source-reconstructed data to examine cortical differentiation of standard versus deviant acoustic processing during a passive auditory oddball task. The spatial activation pattern of 81 atlas regions was correlated dynamically across the time series to assess pattern separation of the two conditions. The sample is comprised of infants who completed a 6-week interactive auditory experience intervention between 4 and 7 months of age (*n=30*), and age-matched controls at 7 months (*n=27*). Intervention infants were operantly conditioned to learn the contingency between increasingly complex deviant stimuli and the paired reward video. Given the heightened experience-dependent sensitivity in this period of development, and the previously observed reduced discrimination latencies in the scalp-evoked signal following intervention, we predicted that post-intervention infants will show greater spatiotemporal pattern separation compared to age-matched controls. The pattern similarity analysis of 4-month-old infants indicate immature processing, with positively correlated (less separated) neural activations to standard and deviant acoustic inputs during the discrimination (r (79) =0.92) and conflict-resolution (r (79) =0.98) periods of perceptual processing. At 7 months of age, increased pattern separation is revealed, with the control group showing strongly differentiated patterns at stimulus onset (r (79) =-0.89). Infants who received the intervention show the greatest spatiotemporal pattern separation in RAP, particularly in the discrimination window (r (79) =-0.003). These results reveal differentiation of sensory input and acoustic mapping in the developing infant brain during RAP. This provides insight into how auditory

perception reshapes acoustic circuitry to support the specialization of function over development. Targeted intervention was shown to influence auditory processing skills, with the trained infants discriminating rapidly presented input at a more differentiated neural state.

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Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: Department of Biology, University of Maryland
Neuroscience and Cognitive Science Graduate Program, University of Maryland
Center for Comparative and Evolutionary Biology of Hearing, University of Maryland
Brain and Behavior Institute, University of Maryland
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Title: Decision-making shapes auditory cortical responses to harmonic complex tones in noise

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Abstract: Background noise creates a challenging acoustic environment for listening. Adaptive plasticity in auditory cortex is thought to facilitate hearing in noise by enhancing neural responses to behaviorally meaningful sounds. However, it remains unclear how auditory cortex supports recognition of perceptual features in noise, such as the pitch of a missing fundamental frequency (F0) harmonic complex tone (HCT). We have recently shown that missing-F0 HCTs evoke structured and experience-dependent periodotopic maps in mouse auditory cortex. We therefore hypothesized that adaptive plasticity in mouse auditory cortex facilitates recognition of missing-F0 HCTs in noise by modulating the activity of F0-selective neurons as background noise levels change. To investigate, we trained CBA × Thy1-GCaMP6s mice on a go/no-go task to distinguish a target missing-F0 (55 Hz) from a non-target missing-F0 (330 Hz) in broadband (4-45 kHz) sine-phase HCTs, presented at 75 dB SPL. Background noise (4-45 kHz) was randomly interleaved across trials at −∞, 65, or 75 dB SPL, corresponding to signal-to-noise ratios (SNRs) of +∞ (silence), +10, or 0 dB. Using two-photon calcium imaging, we recorded activity from excitatory neurons in layer 2/3 of auditory cortex as mice performed the missing-F0 discrimination task. Mice successfully discriminated target from non-target F0s in silence (d'>1), with performance declining as SNR decreased. Average neural responses to HCTs also declined with decreasing SNR, but tended to be greater during correct vs incorrect behavioral choices. In addition, single-trial population activity encoded both F0 and behavioral choice, outperforming

single neurons by providing greater separation between target and non-target responses. To test whether auditory cortex is necessary for task performance, we also trained Vglut-Cre × Ai40-ArchT mice on the same task and used photostimulation to suppress excitatory neurons across auditory cortex. Preliminary results suggest that optogenetic suppression perturbs task performance. Together, these experiments indicate that auditory cortical responses reflect both perceptual and decision-making processes supporting recognition of behaviorally relevant pitch cues in challenging acoustic environments.

Disclosures: J. Putnam: None. **N.A. Francis:** None.

Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH R00 DA059024

Title: Cortical cell assemblies encoding higher-order computations reactivate during auditory learning

Authors: *C. SHUAI[1], C. DRIEU[2,1];
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Abstract: Offline reactivation of task-related neural activity is thought to support memory consolidation and learning-related plasticity across cortical and subcortical circuits. In sensory cortex, post-task reactivation of cue-evoked population activity has been linked to subsequent changes in sensory representations and to hippocampal-cortical dialogue. However, it remains unclear how offline reactivations in sensory cortex evolve over the course of learning and whether reactivated ensembles preferentially recruit neurons encoding higher-order learning signals. We investigated cell assemblies in the auditory cortex as mice learned an auditory go/no-go discrimination task (Drieu et al., 2025). A group of mice (n=4, learning) learned to lick to the target tone to receive a water reward and withheld from licking to the foil tone to avoid a timeout, while a distinct group (n=3, passive) was presented with identical stimuli over the same extent of time without reinforcement. Longitudinal two-photon calcium imaging tracked the same neuronal populations across the full course of learning (n=1620 in learning mice; n=2339 in passive mice). Tensor component analysis of task-period activity previously identified two higher-order signals causally linked to learning: a reward prediction signal which emerges rapidly and drives early task acquisition, and an action suppression signal, which contributes to later improvements in performance. To characterize offline population dynamics independently of strong feedforward sensory drive during behavior, we identified highly synchronous events (HSEs) and cell assemblies from post-task spontaneous activity using a PCA/ICA-based framework. While HSE occurrence was comparable between learning and passive mice,

assembly activation rates were higher in the learning group. Assemblies with greater task-evoked activation were more strongly reactivated during offline periods. Notably, we found that a subset of post-task assemblies in learning mice was enriched in RP neurons. These assemblies were expressed during both task and post-task periods, and their expression varied across learning. Ongoing analyses are testing whether post-task expression of RP or action suppression-enriched assemblies is related to learning state and behavioral improvement. Together, these findings suggest that associative learning selectively enhances offline reactivation of auditory cortical ensembles enriched in reward prediction signals, raising the possibility that offline sensory cortical dynamics contribute to the consolidation of learned stimulus-action associations.

Disclosures: C. Shuai: None. **C. Drieu:** None.

Poster

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Title: Auditory evoked potentials across human thalamic nuclei during passive listening and auditory attention

Authors: *A. N. SIMMONS[1,2,3,4], S. KASTNER[6], J. T. WILLIE[7,1,3,5,8], P. BRUNNER[2,1,3,5]; [1]Washington Univ. in St. Louis, St. Louis, MO; [2]Dept. of Neurosurg., [3]Div. of Neurotechnology, Washington Univ. in St. Louis Sch. of Med., St. Louis, MO; [4]Natl. Ctr. for Adaptive Neurotechnologies, St. Louis, TX; [5]Natl. Ctr. for Adaptive Neurotechnologies, St. Louis, MO; [6]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [7]Neurolog. Surgery, Washington Univ. Sch. of Med., Saint Louis, MO; [8]Dept. of Neurosurg., Univ. of Texas at Austin, Austin, TX

Abstract: The thalamus comprises numerous functionally heterogeneous sub-nuclei that regulate a broad range of cognitive processes, including sensory processing and attention. Although thalamic contributions to visual perception have been extensively studied, less is known about how individual thalamic nuclei participate in auditory perception. In this study, we characterized auditory evoked potentials (AEPs) across multiple thalamic nuclei using stereoelectroencephalography(SEEG) electrode recordings obtained from eleven adults with drug-resistant epilepsy undergoing clinically indicated intracranial monitoring. Across subjects, we recorded electrophysiological activity from multiple higher-order nuclei, including the centromedian nucleus (CM), anterior nucleus of the thalamus (ANT), ventral anterior nucleus (VA), and medial and inferior pulvinar (PuM and PuI). Participants completed two paradigms that differed in auditory attention demands - a passive task where subjects were asked to listen to recordings of spoken words or non-word sounds (Word/Non-word task) and an active task where they were instructed to locate visual cues and received auditory-only feedback on the accuracy of their response (Egly-Driver task). For the Word/Non-word task, each trial consisted of a 0.7-second auditory stimulus followed by a 1-second silent (baseline) period. Stimuli consisted of 64 words and 64 non-words delivered through speakers. For the Egly-Driver task, subjects completed 200 trials, each of which included a visual cue presented on a screen and a button press to indicate the location of the cue, followed by a high or low tone indicating whether the response was correct. No visual cues were shown during auditory feedback. We analyzed neural activity time-locked to the onset of auditory cues. Between these two paradigms, we characterized thalamic responses to auditory stimuli across a range of attention states. We observed robust AEPs across all sampled thalamic nuclei. Notably, AEPs were significantly stronger during passive listening than during auditory feedback in the attention task across all thalamic nuclei except the PuM (Wilcoxon Ranksum, $p<0.05$). These findings are consistent with prior evidence that thalamic responses are strongly modulated by behavioral state and attentional context. Together, these results provide a comparative characterization of the physiological dynamics of neuronal activity across multiple human thalamic nuclei during distinct attentional states. This work advances our understanding of the physiological mechanisms through which the human thalamus supports auditory perception and attention.

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Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R21 DC021520
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Title: Age-related degradation of sensory encoding and functional circuit interactions in auditory cortex

Authors: *H. KANG[1], P. O. KANOLD[2];
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Abstract: Aging is associated with declines in auditory perception that cannot be fully explained by peripheral hearing loss alone. Even when peripheral hearing remains relatively intact, older individuals often experience difficulty processing complex acoustic scenes, suggesting age-related impairments in central auditory processing. Efficient auditory perception relies on rapid neural adaptation and the ability of cortical circuits to encode recurring sensory information. However, the impact of aging on these rapid cortical encoding mechanisms remains poorly understood.Here, we investigated how aging affects neural representations of complex sounds and local circuit dynamics in the auditory cortex comparing aging mice with young adult mice. Using in vivo two-photon calcium imaging in awake mice, we imaged neuronal activities from populations of neurons using in vivo two-photon imaging in response to dynamic random chord (DRC) stimuli containing re-occurring and random acoustic patterns. To causally probe local network interactions, we combined functional identification of frequency-selective neurons with targeted holographic stimulation of co-tuned neuronal ensembles.Aging mice exhibited reduced sound-evoked response amplitudes and weaker adaptation to re-occurring acoustic patterns. Population analyses further revealed altered network organization in aged auditory cortex, characterized by reduced stimulus-dependent correlation and difference between re-occurring and random sound representations. Furthermore, holographic stimulation of functionally selective neuronal ensembles produced robust network-level suppression of co-tuned neurons in young adults, consistent with rapid activity rebalancing within local circuits. In contrast, aging mice showed significantly weaker stimulation-induced network modulation despite reliable activation of targeted neurons, indicating impaired circuit-level regulation.Together, these findings demonstrate that aging disrupts sensory encoding ability largely due to reduced local network dynamics in the auditory cortex. Reduced adaptive modulation and weakened functional interactions within cortical circuits may limit the ability of aged auditory systems to efficiently represent and segregate complex acoustic information, providing characteristics of altered cortical mechanisms underlying age-related deficits in auditory perception.

Disclosures: H. Kang: None. **P.O. Kanold:** None.

Poster

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Program #/Poster #: PSTR275.19/EE11

Topic: E.05. Auditory and Vestibular Systems

Support: The Hong Kong Polytechnic University Research Postgraduate Scholarship (author Y.C.)

Title: Modulating Theta-gamma Cross-Frequency Coupling With Auditory Entrainment in Older Adults With MCI: Implications for Working Memory

Authors: *Y. CHEN[1], C. HSU[1], D. G. TAN[1], L. LAM[2,1], K. LIU[1];
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Abstract: Working memory often declines in older adults and is particularly affected in MCI, where related difficulties threaten independence and increase healthcare burden. Safe and accessible interventions that can support working memory are therefore of significant clinical importance. In our pilot study, we examined whether frequency-specific auditory entrainment modulates theta-gamma cross-frequency coupling and relates to working memory performance in older adults with MCI. Twelve participants (71.25 ± 0.93) received two auditory stimulation conditions (3 + 40 Hz and 40 Hz alone) for 120 seconds while EEG was recorded. They were asked to complete the Digit Span Backward (DSB) to assess their working memory. We examined theta-gamma phase-amplitude coupling (quantified using the modulation index) in functional connectivity across predefined regions and calculated its correlations with working memory performance. We selected 13 brain regions predefined in previous work. Compared with 40 Hz stimulation, 3 + 40 Hz stimulation induced stronger theta-gamma cross-frequency coupling, particularly in connectivity involving the left-parietal region. The results are reported in the graphic. We used the left-parietal region as the central ROI for FDR correction across the other predefined ROIs. All results remained $p < 0.05$ after FDR correction. Moreover, coupling during 3 + 40 Hz stimulation was moderately and positively correlated with working memory performance, indicating a behaviorally meaningful neural modulation. Correlations were observed for connectivity between the left-parietal and prefrontal regions ($r = 0.597$, $p = 0.040$, $n = 12$), between the left-parietal and right-temporal regions ($r = 0.627$, $p = 0.029$, $n = 12$), and between the left-parietal and parietal regions ($r = 0.578$, $p = 0.049$, $n = 12$). Importantly, the 3 + 40 Hz protocol was better tolerated than 40 Hz stimulation. Our study highlights 3 + 40 Hz auditory stimulation as a promising, well-tolerated approach for targeting oscillatory mechanisms underlying working memory in older adults with MCI.

Table 2. Modulation Index Across Functional Connectivity During 3 + 40 Hz and 40 Hz Auditory Stimulation

		A_{3+40}	A_{40}			
Left-parietal	Brain Regions	MI	MI	t (12)	*p*	Cohen's d
Connected With	Prefrontal	19.860 ± 0.039	19.556 ± 0.393	2.695	0.021*	0.390
	Frontal	19.856 ± 0.032	19.564 ± 0.393	2.647	0.023*	0.382
	Right-frontal	19.866 ± 0.044	19.574 ± 0.366	2.805	0.017*	0.359
	Left-central	19.864 ± 0.032	19.594 ± 0.354	2.701	0.021*	0.347
	Central	19.857 ± 0.032	19.566 ± 0.402	2.548	0.027*	0.396
	Right-central	19.861 ± 0.035	19.602 ± 0.370	2.434	0.033*	0.369
	Left-temporal	19.859 ± 0.016	19.571 ± 0.386	2.615	0.024*	0.382
	Right-temporal	19.854 ± 0.023	19.579 ± 0.387	2.485	0.030*	0.384
	Parietal	19.857 ± 0.036	19.567 ± 0.412	2.471	0.031*	0.407
	Right-parietal	19.860 ± 0.029	19.580 ± 0.364	2.673	0.022*	0.362
	Occipital	19.855 ± 0.027	19.576 ± 0.383	2.524	0.028*	0.383

* $p < 0.05$
A_{3+40}: 3 + 40 Hz Auditory Stimulation; A_{40}: 40 Hz Auditory Stimulation; MI: Modulation Index

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Poster

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Title: Acoustic rearing scales auditory cortical information processing while preserving a music-aligned temporal profile

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Abstract: How acoustic experience shapes cortical processing of musical temporal structure remains poorly understood. We addressed this in rat primary auditory cortex by asking whether developmental acoustic rearing changes temporal information processing and whether the resulting cortical profile aligns with music. Multi-unit activity was recorded under urethane anesthesia during Bernoulli click trains, and information processing capacity (IPC) quantified how well recent stimulus history could be linearly read out from population activity, yielding lag-by-order maps. Male Wistar rats were reared as naive controls (n=16) or exposed to Mozart's K.448 (n=9), a pitch-shuffled version (n=6), or a rhythm-shuffled version (n=5) for at least 4 weeks, 6 h/day, and recordings were made at 11-14 weeks of age. Across animals, rearing condition altered the first-order IPC profile, with generally larger IPC in exposed rats than in naive controls. Exposure-related increases in total IPC were concentrated at longer inter-stimulus intervals, especially 300 ms, near the stimuli's inter-note timescale, whereas short intervals showed little change. When exposed groups were pooled, the nonlinear fraction of IPC was larger than in naive controls. Second-order IPC maps also showed exposure-related enhancement, but the loci of enhancement were similar across the three exposed groups despite disruption of pitch or rhythm, suggesting that rearing scaled the amount of cortical information processing more than the layout of the lag-by-order map. We next compared auditory IPC with a music-side higher-order autoregressive projection (HARP): the R^2 with which the current onset signal is explained by regression on its own past values and their pairwise products, the same

read-out as IPC applied to the stimulus. HARP profiles varied across composers and historical periods, with stronger cortical-musical correspondence for Baroque and Classical pieces. This correspondence was carried by the radial (lag-distance) profile and the slope of that profile; after removing this radial profile, the residual off-diagonal (cross-lag) structure showed little systematic correspondence. Together, these results suggest that acoustic rearing scales the amount and nonlinear share of cortical information processing without substantially reshaping its temporal layout, and that auditory cortex and music align mainly through a shared radial profile rather than fine-grained off-diagonal structure.

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Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

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Program #/Poster #: PSTR275.21/EE13

Topic: E.05. Auditory and Vestibular Systems

Title: The Impact of Sleep Deprivation on Psychosis-like Perception in Mice

Authors: *N. K. ZERNICKA-GLOVER[1], F. TEIXEIRA SUBTIL[1], A. VIDUOLYTE[1], J. MACRAE[1], K. SCHMACK[2];
[2]Dept. of Psychiatry and Psychotherapy, [1]Francis Crick Inst., London, United Kingdom

Abstract: Sleep deprivation can trigger psychosis-like states, including altered perception reflected in auditory hallucinations, yet the underlying mechanisms are unclear. Dopaminergic signalling is disrupted after sleep deprivation and associated with psychosis. We therefore hypothesised that sleep deprivation leads to psychosis-like perception through striatal neuromodulatory signalling. To test this, we established a sleep-deprivation paradigm where mice are prevented from sleeping through motion. To establish whether this paradigm induced effects on behaviour, we measured prepulse inhibition and open-field locomotion. Psychosis-like perception was assessed using an established task where mice report tones and express confidence by waiting for reward. Hallucination-like percepts (HALIPs) are defined as high-confidence false alarms. Utilising dual-colour fiber photometry, we relate the temporal dynamics of serotonin and dopamine in striatum during HALIPs. To relate sleep deprivation to neuromodulatory state, we conducted mass spectrometry metabolic profiling of neural tissue and cerebrospinal fluid. Sleep-deprived mice showed altered prepulse inhibition (paired t-test: $t(14)=-3.99$, $p<.01$) and initial hyperlocomotion (repeated measures ANOVA, main effect: $F(1,29)=19.06$, $p<.001$), validating our paradigm. Remarkably, sleep-deprived mice reported more HALIPs (linear mixed effects model: $F(1,82)=5.8$, $p<.05$), demonstrating increased psychosis-like perception. This was accompanied by increased false alarm confidence (linear mixed effects model: $F(1,91)=8.9$, $p<.01$, $n=4$), suggesting sleep loss affects perceptual confidence rather than response bias or overall accuracy. Preliminary metabolomic profiling

revealed alterations in neuromodulatory and related metabolic pathways, including increased kynurenine within the schizophrenia-associated kynurenine pathway (ANOVA, main effect: $F(1,18)=7.25$, $p<.05$), which may influence striatal signalling. Together, our results indicate sleep deprivation induces psychosis-like perception and point to altered metabolic pathways as a mechanism linking sleep deprivation to neurotransmitter dynamics and behaviour. Ongoing fibre photometry experiments investigate serotonin and dopamine's role in these perceptual alterations. By integrating in vivo neurotransmitter measurements with metabolic profiling, we aim to identify mechanisms linking sleep deprivation, altered neuromodulatory state, and perceptual disturbances. Ultimately, we hope to build our understanding of the neural underpinnings of perception and how sleep shapes subjective experience.

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Poster

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Topic: E.05. Auditory and Vestibular Systems

Title: The role of striatal acetylcholine in hallucination-like perception

Authors: *A. VIDUOLYTE[1], K. FARRELL[3], N. ZERNICKA-GLOVER[1], M. BOSC[4], K. SCHMACK[2];
[2]Dept. of Psychiatry and Psychotherapy, [1]Francis Crick Inst., London, United Kingdom; [3]The Francis Crick Inst., London, United Kingdom; [4]Kepecs Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Hallucinations, a cardinal feature of psychosis, are perceptions not grounded in external reality. While the exact mechanisms of these experiences remain elusive, recent clinical trials of novel antipsychotic treatments suggest a link between the neuromodulator acetylcholine and psychotic symptoms. Acetylcholine is abundant in the striatum, where it can interact with dopamine, a neuromodulator known to be elevated during psychosis. This suggests that striatal acetylcholine might play a crucial role in hallucinations. Our work aims to elucidate how striatal acetylcholine is involved in unfounded perceptions in mice and its interplay with dopamine.
We model hallucinations in mice using the hallucination-like perception (HALIP) task (Schmack et al., 2021). In this task, mice are trained to report presence or absence of an auditory signal embedded in a noisy background and express confidence in their decision by waiting for a reward. A hallucination-like percept is defined as a high confidence false alarm - a report of a signal when no signal was present. Using dual-color fiber photometry, we measure temporal dynamics of acetylcholine and dopamine in mouse auditory striatum ($N = 6$) during hallucination-like perceptions.
We found that both acetylcholine and dopamine showed robust yet distinct responses to reward

delivery, confirming the success of our dual-color approach. On signal trials, both neurotransmitters also exhibited stimulus-locked responses that scaled with signal volume, indicating a shared contribution to the encoding of sensory evidence. We also observe that on no-signal trials reported as signal (false alarms), dopamine activity was akin to that of signal trials and scaled with time investments. Meanwhile, acetylcholine levels on the same no-signal trials exhibited an elevated peri-stimulus baseline which was predictive of a signal choice. This suggests that both neurotransmitters play a role in hallucination-like perceptions: when a no-signal stimulus is presented but a signal is perceived, it is preceded by higher acetylcholine levels indicative of sensory expectation, followed by phasic signal-locked dopamine responses indicative of sensory response. To test the causal contribution of acetylcholine to false signal perceptions, ongoing experiments employ optogenetic stimulation of cholinergic neurons in the auditory striatum paired with pharmacological interventions.
Together, our experiments suggest that shifts in acetylcholine transmission may give rise to hallucination-like experiences in mice. This will pave way for untangling the neural mechanisms by which novel antipsychotic treatments might take their effect.

Disclosures: A. Viduolyte: None. **K. Farrell:** None. **N. Zernicka-Glover:** None. **M. Bosc:** None. **K. Schmack:** None.

Poster

PSTR275: Auditory Perception and Cognition in Humans and Animals

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR275.23/EE15

Topic: E.05. Auditory and Vestibular Systems

Title: Establishing A Head-Fixed Auditory Detection Task For Circuit-Level Investigation of Hallucination-like Perception

Authors: *A. E. BUNBURY[1], K. SCHMACK[2], M. BOSC[3], M. F. SANTOS[4];
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Abstract: Hallucinations can have a debilitating impact on psychosis patients' lives, yet available treatments show limited efficacy and approximately a third of patients remain treatment-resistant. Identifying novel treatment targets requires a circuit-level mechanistic understanding, which is inaccessible in humans with non-invasive methods alone. A translational auditory detection task, in which high-confidence false alarms (HALIP) serve as a behavioural proxy for hallucinations, developed and validated across humans and freely-moving mice (Schmack et al., 2021), enables circuit-level investigations of hallucinations in rodent models. However, freely-moving designs do not allow for the use of advanced circuit investigations. Therefore, we established a head-fixed version of the HALIP task, enabling acute electrophysiological recordings and precise circuit manipulation during hallucination-like

behaviour. In our head-fixed HALIP task, mice controlled the position of visual gratings displayed on a screen by turning a wheel. Mice self-initiated trials by moving an initial grating to the centre of the screen. On each trial, mice were then presented with an auditory stimulus which was either a tone embedded in the background noise (signal trial), or background noise only (no-signal trials), with trial types randomly interleaved. Following stimulus presentation, two new gratings appeared, and mice reported the presence or absence of the tone by moving the left or right grating to the centre. Correct responses were rewarded with water via a lick spout after a variable delay. Mice progressed through pre-defined training stages and were considered to have learnt the task upon achieving >70% accuracy. Five of six mice successfully learned the task, reaching a mean accuracy of 72.9% ± 1.9 (mean ± SEM) within 36.6 ± 3.3 sessions. Choices followed a psychometric function, with hit rate increasing with signal intensity (all $R2 > 0.99$, all $P < 0.001$), indicating that choice behaviour was driven by sensory evidence. Mice exhibited a false alarm rate of 12.9 ± 2.5%, comparable to the false alarm rate observed in a freely-moving cohort 13.9% ± 2.0 %.These results establish a head-fixed paradigm that recaptures key behavioural signatures of the freely-moving HALIP task, providing a platform for acute electrophysiological recordings and circuit manipulations during hallucination-like behaviour. Thereby, we hope to enable advances in the circuit-level understanding of hallucinations needed to advance treatments for psychosis.

Disclosures: A.E. Bunbury: None. **K. Schmack:** None. **M. Bosc:** None. **M.F. Santos:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.01/EE16

Topic: F.04. Voluntary Movements

Support: NRF Grant RS-2024-00398768
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KIST Grant 26E0131

Title: Role of neurotensin-specific corticothalamic circuits in the selection of competing innate actions

Authors: *Y. PARK[1,2,3], Y. JANG[1,4,3], Y. KIM[1,4,3], A. SERIKOV[1,2], J. KIM[1,2];
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Abstract: When survival demands conflict—such as the simultaneous need to feed and avoid predators—the brain must rapidly resolve competing innate drives to execute an appropriate

action. Yet the neural circuits that resolve such action conflicts remain largely unknown. Here, we developed a new loom/feed test to observe the conflict between naturally induced fear and feeding and identified a novel anterior cingulate cortex (ACC) output to the ventral anterior and ventral lateral thalamus (VA/VL) that adjusts the selectivity between these innate actions. Using micro-endoscopy and fiber photometry, we revealed reduced corticofugal activity and thalamic initiation related signals for less preferred actions during unbalanced periods, suggesting that ACC-thalamic circuits may be involved in regulating behavioral choices. Accordingly, the optoinhibition of ACC-thalamic circuits induced feeding bias at the expense of defense. To identify upstream “commander” cortical cells gating this output, we established dual-order tracing (DOT)-translating ribosome affinity purification (TRAP) and found a novel population of neurotensin-positive interneurons (ACCNts). Photoexcitation of ACCNts neurons caused similarly hyper-selective behaviors. Together, these findings establish a 'corticofugal action filter', providing a circuit-level understanding of how cingulate-thalamic circuit resolves competition between innate actions.

Disclosures: Y. Park: None. **Y. Jang:** None. **Y. Kim:** None. **A. Serikov:** None. **J. Kim:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.02/EE17

Topic: F.04. Voluntary Movements

Support: NIH 5R01NS123396

Title: Microcircuit basis for projection neuron specific engagement of gamma rhythms in primary motor cortex

Authors: *D. KIM[1], D. B. HEADLEY[2];
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Abstract: Oscillations occurring within the primary motor cortex (M1) at frequencies in the gamma band (30-80 Hz) are associated with skilled motor movements. While this phenomenon is well documented across animal and human subjects, its recruitment of projection neuron subtypes has received little attention. Our work addresses this question by investigating the propensity of four M1 projection neuron (PN) subtypes to promote and entrain to gamma: layer 2/3 intratelencephalic (L2/3 IT), layer 5 pyramidal tract (L5 PT) and cross-corticostriatal (CCS), and layer 6 corticothalamic (L6 CT) neurons. A growing body of literature suggests that PT neurons are more strongly linked to gamma and that their connectivity is more suitable for supporting fast oscillations than IT or CT neurons. We thus hypothesized that PT neurons will show the strongest tendency to entrain to and support gamma among the four M1 PN subtypes. To test this, we first examined the anatomical connectivity between the PN subtypes and fast-

spiking parvalbumin-positive (PV+) interneurons, who are crucial players in the generation and maintenance of cortical gamma. In PV-cre transgenic rats, we labeled the presynaptic terminals of PV+ interneurons with AAV1-Flex-tdTomato-SypEGFP and the somata of PNs with retrograde tracers fast blue and CTB-Alexa647 in a projection-specific manner. This allowed us to visualize, quantify, and compare the density of synaptic inputs each subtype receives from PV+ interneurons. Second, we examined the PNs' proclivity to induce M1 gamma with optogenetic and patch clamp methods in ex vivo slice preparations. Specifically, we expressed the excitatory opsin ChroME in the somata of each subtype and delivered ramping blue light stimuli to elicit gamma in the local network. Simultaneously, whole-cell patch current clamp recordings were obtained from adjacent opsin-negative neurons. This allowed us to measure the gamma power of oscillations driven by each PN subtype. In ongoing experiments, retrograde tracers are utilized alongside the aforementioned optogenetic methods to target and record from PNs of each subtype, enabling comparison of their entrainment to elicited rhythms. Optogenetic activation of PT neurons elicited the strongest gamma compared with the other subtypes. This work reveals projection subtype-specific propensities for gamma entrainment in M1, with PT neurons potentially exhibiting the most robust involvement, thereby deepening our understanding of the microcircuit mechanisms underlying motor control.

Disclosures: D. Kim: None. **D.B. Headley:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.03/EE18

Topic: F.04. Voluntary Movements

Title: Neuronal Dynamics During Voluntary and Forced Locomotion in Primary Sensory Cortex

Authors: *A. K. PIMENTEL FARFAN[1], G. LOEWINGER[2], E. PARK[1], A. R. INACIO[3], M. HAN[1], F. PEREIRA[2], S. LEE[1];
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Abstract: Behavioral states strongly modulate neuronal activity across multiple brain areas. Spontaneous locomotion engages subsets of neurons that exhibit stable activity patterns. However, it remains unclear whether voluntary and externally driven movements engage similar or distinct neural populations. Voluntary and forced locomotion may differ not only in sensory feedback, but also in behavioral state, motor control, and sensorimotor congruence. Comparing these conditions can reveal which components of primary somatosensory cortical activity are common across locomotion conditions and which depend on how movement is generated. To test this, we used two-photon calcium imaging to record large populations of pyramidal neurons in the primary somatosensory cortex of head-fixed mice during voluntary and forced running. In voluntary trials, mice freely initiated and terminated running. In forced trials, wheel movement

was controlled by a motor, while a gear prevented mice from moving the wheel independently. Preliminary results suggest that voluntary and forced locomotion engage overlapping but partially distinct neuronal populations. During voluntary locomotion, a subset of neurons was modulated by running, whereas forced locomotion recruited both these neurons and additional neurons that were not engaged during voluntary running. Ongoing analysis combines longitudinal functional regression with clustering to identify groups of neurons with distinct temporal relationships between running speed and neural activity. These findings may provide insight into how cortical circuits adapt their activity depending on motor intent and external control, with broader implications for understanding sensorimotor integration and motor disorders.

Disclosures: A.K. Pimentel Farfan: None. **G. Loewinger:** None. **E. Park:** None. **A.R. Inacio:** None. **M. Han:** None. **F. Pereira:** None. **S. Lee:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

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Title: Cortical-striatal attractors conjoin for self-paced movement sequences

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Abstract: Voluntary movement sequences, from typing to playing an instrument, require the flexible chaining of discrete motor acts into coherent behavioral episodes. How cortical and subcortical circuits jointly encode and protect sequence integrity remains unresolved. Here, we show that motor cortex (M1) and dorsal striatum implement complementary attractor dynamics that together gate the precise execution of self-paced motor sequences in mice. Using high-density electrophysiology and circuit-specific optogenetics during a learned rapid-sequence task, we identify co-activated but functionally distinct M1 and striatal population subspaces: M1 dynamics are transient and strongly encode sequence initiation, whereas striatal dynamics are sustained and persist across the full sequence duration. Closed-loop force-field perturbations of ongoing movement reveal an integrator-like attractor dimension selectively in striatal, but not M1, population geometry, a signature absent when animals internally generate erroneous

sequences. These findings reveal a division of labor in cortico-striatal circuits where M1 provides a rapid, initiation-gating signal, while the striatum maintains an ongoing error-correcting attractor that enforces moment-to-moment sequence fidelity. Our results establish that conjoint cortical-striatal attractor states, rather than a single locus of motor control, underlie the contextual precision of learned action sequences.

Disclosures: H. Khan: None. **K. Jayant:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Program #/Poster #: PSTR276.05/EE20

Topic: F.04. Voluntary Movements

Support: NIH RF1 NS132025
1S10OD030243-01

Title: Brain-wide contextual states shape cortical-subcortical dynamics for flexible and robust motor planning

Authors: *W. N. ZHANG[1], N. LI[2];
[2]Neurosci., [1]Duke Univ., Durham, NC

Abstract: Adaptive behavior requires the ability to flexibly select appropriate actions across changing task demands. Classical motor neuroscience has largely focused on single-task paradigms, leaving unclear how the brain selects motor strategies across changing contexts and uses them to guide flexible action. Here, we investigate how task context shapes preparatory activity before movement onset, a key stage for selecting and initiating goal-directed actions. We developed a behavioral paradigm in which mice flexibly selected between distinct action strategies to obtain water rewards: directional licking or directional reach-grasp-drinking. Using cortex-wide scanning photoinhibition, we identified frontal cortical regions overlapping with anterior lateral motor cortex (ALM) that are required for motor preparation for both licking and reaching. Within ALM, spatially intermingled but functionally distinct neuronal populations encoded future movement direction for licking and reaching. Depending on task context, preparatory activity evolved toward two discrete action-specific states: lick-left or lick-right in the licking context, and reach-left or reach-right in the reaching context. These context-dependent dynamics were robust to transient bilateral optogenetic perturbations of frontal cortex: perturbations disrupted ongoing activity and scrambled upcoming left-right choices, yet neural trajectories recovered toward action states appropriate for the current context. Thus, although the full task space contained four possible action states, only the two states appropriate for the current context were available on any given trial. We further found that task context itself was robustly encoded in baseline single-neuron activity before trial onset, consistent with a persistent network state. In ALM, neurons with strong baseline context selectivity were preferentially

recruited into subsequent motor-preparatory dynamics, suggesting a mechanism linking contextual information to action selection. Moreover, this brain-wide contextual state flexibly reconfigured functional coupling and communication subspaces within a cortico-subcortical motor-planning network spanning ALM and superior colliculus. Our results support a hierarchical model of flexible motor control in which a global contextual signal selects a motor strategy, while context-dependent cortical-subcortical dynamics guide the selection and stabilization of specific motor plans within that strategy.

Disclosures: W.N. Zhang: None. **N. Li:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

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Title: Inter-regional communication geometry drives the regional dynamical reorganization during complex skilled movements

Authors: E. NAGASE[1], E. STENZLER[2], N. JEONG LEE[2], D. LIPKIN[2], ***A. ARAC**[2]; [1]UCLA, Los Angeles, CA, ; [2]UCLA, Los Angeles, CA

Abstract: Skilled behavior requires neural circuits to implement qualitatively different computations at successive moments without external instruction, yet how a distributed circuit coordinates these transitions across regions remains unknown. We recorded simultaneously from ten cortical and subcortical regions spanning the cortico-basal ganglia-thalamo-cerebellar motor circuit using six Neuropixels probes in mice performing a learned reach-grasp-consume task. Markerless 3D kinematic analysis segmented the behavior into six distinct phases defined by paw position and shape. Applying switching linear dynamical systems to each region independently, we found that every region organized its population dynamics into discrete neural phases, but with region-specific granularity that was predicted by each region's intrinsic dynamical timescale. Neural transitions preceded behavioral transitions in all regions, indicating internally generated rather than feedback-driven switching. Characterizing the phase-specific dynamics matrix revealed a fundamental dissociation: cortical regions substantially restructured their dynamics matrix at each phase transition, resulting in large Frobenius distance, while subcortical regions shifted their operating point without restructuring, with small Frobenius distance despite large subspace rotations. Communication subspace analyses across all directed region pairs revealed three mechanistically distinct communication strategies driving this dissociation: source-specific input reorganization (selective routing) in cortex, uniform gain

scaling (broadcast gating) in striatal and thalamic regions, and communication subspace rotation (geometry reorganization) in pallidal-cerebellar regions. The secondary motor cortex (M2) was identified as the primary driver of the primary motor cortex's (M1) phase-specific restructuring. Multi-regional RNN modeling predicted that M2 inhibition would disrupt M1 dynamics specifically at the fast transport phase. Closed-loop optogenetic inhibition of M2 confirmed this prediction, disrupting M1 trajectories and causing categorical reach abandonment when applied before grasp but having no effect after grasp. These results establish that sequential neural computation is implemented through region-specific dynamical reorganization determined by inter-regional communication geometry, not by regional identity, a principle that may generalize across neural systems.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

Support: NIH Grant 5R01NS123396

Title: Modulation of effective synaptic connectivity in primary motor cortex by rhythmic activities in vivo

Authors: *D. B. HEADLEY[1], D. KIM[3], T. QIU[2];
[2]Ctr. for Mol. and Behavioral Neurosci., [1]Rutgers, The State Univ. of New Jersey, Newark, NJ;
[3]Rutgers, The State Univ. of NJ - Newark, Newark, NJ

Abstract: Cortical computation arises from microcircuitry, with connectivity between neuron pairs varying with spatial separation, cortical layer, cell class, and coding properties. In primary motor cortex (M1), many studies relate synaptic connections to these factors, but connectivity operates within an active network whose dynamics may alter effective coupling. A key mechanism is feedback inhibition: fast-spiking, parvalbumin-positive interneurons receive convergent input from nearby pyramidal neurons and provide divergent perisomatic inhibition in return. This reciprocal loop generates an inhibitory rhythm above 40 Hz (gamma). In M1, gamma rhythms often accompany movement onset, when intrinsic circuit dynamics are thought to shape the activity patterns that drive specific motor actions, underscoring the need to understand how gamma modulates circuit function.We examined gamma rhythms in rat M1 during a reaching task and their role in regulating synaptic strength between pyramidal neurons. Using Neuropixel 2.0 probes, we recorded neural activity during exploratory reaching and isolated single units with Kilosort 4.0. Putative monosynaptic excitatory connections were identified via cross-correlation as pairs showing a sharp (<3 ms) peak at short latency (<5 ms)

after presumed presynaptic spikes. All animals showed an LFP power peak around 50 Hz, and single-unit spike timing was entrained to this rhythm. Our connectivity criteria were validated by expected cortical microcircuit properties: connection probability decreased with intersomatic distance (most within <100 μm), was biased from superficial to deeper layers, and showed strong convergence onto fast-spiking units, consistent with their classification as interneurons.We quantified excitatory connection effectiveness as the height of the cross-correlation peak normalized by the mean firing rates of the pre- and postsynaptic neurons. The strength of these excitatory connections depended systematically on the phase and amplitude of local gamma oscillations. Across the gamma cycle, synaptic efficacy alternated between enhancement and suppression, and the magnitude of this phase-dependent modulation increased with gamma power. Together, these findings demonstrate that the functional efficacy of M1 microcircuitry is not static but dynamically fluctuates in concert with ongoing gamma-band activity.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

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Topic: F.04. Voluntary Movements

Support: NSF NRT 2152260
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NIH T32 MH082174
R01 MH124818

Title: Cortical and subcortical contributions to flexible evidence evaluation

Authors: *K. STEWART[1], R. CHAUDHURI[2], T. D. HANKS[3];
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Abstract: The ability to flexibly accumulate sensory evidence over time is essential for adaptive behavior. Often, noisy sensory evidence is acquired sequentially in time until a choice commitment threshold is reached. Brain regions thought to be involved in this process have long been investigated, including the rodent frontal orienting fields (FOF), posterior parietal cortex (PPC), anterior dorsal striatum (ADS), and superior colliculus (SC). However, the function of these brain regions has predominantly been studied in discrimination tasks, where the statistics of the stimuli giving rise to the evidence is constant. Yet, these statistics often change, leading us to weigh evidence differently as a function of time. The role they play flexible decision making is unclear. Here, we probe the role these cortical and subcortical regions play in decision requiring dynamic evidence evaluation using a rodent change detection task. Adult rats were trained to

detect increases in auditory click rates drawn from a stochastic Poisson process and to report those changes through an orienting movement. To test the contribution of these regions to free response decision processes, we used the GABA agonist muscimol to perform reversible pharmacological inactivation of an individual region while rats performed the change detection task. Previous work from the Hanks laboratory suggests that inactivation of PPC led to slower responses and evidence evaluation, suggesting PPC may be involved in modulating decision timing. Intriguingly, whole-session bilateral FOF inactivation led to increased decision responsiveness compared to control sessions, suggesting FOF contributes to shaping free response decision by playing an active role in withholding decision commitment during deliberation. Inactivation of ADS had effects similar to that of FOF, with an increase in responsivity and reaction time. Psychophysical reverse correlation analyses revealed a change in the amount of evidence required for detection reports with inactivation of ADS compared to control, suggesting that ADS may be an important region for evidence evaluation. Inactivation of SC resulted in a rightward shift of the psychophysical reverse correlation kernel, in line with hypotheses that the SC is an important brain region for decision termination. Taken together, our results contribute to our understanding of shared and region-specific contributions of the distributed decision making network to free response decisions.

Disclosures: K. Stewart: None. **R. Chaudhuri:** None. **T.D. Hanks:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Support: NICHD/NIH T32HD040127
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NINDS/NIH 5R01NS118030

Title: Selective coupling and decoupling prepare distributed brain networks for skilled action

Authors: *S. M. LEMKE, S. APPAQAQ, J.-Z. GUO, A. W. HANTMAN;
Univ. of North Carolina, Chapel Hill, NC

Abstract: The precise and rapid nature of skilled actions has motivated a long-standing theory that preparatory neural states must emerge to enable upcoming actions. This has been best characterized in motor cortex, where neural activity evolves toward an initial state that governs subsequent cortical dynamics. Yet complex actions require coordination across multiple areas beyond motor cortex, and how this distributed network prepares remains unknown. We recorded over 40,000 neurons across the brain as mice produced skilled reach-to-grasp actions, revealing selective coupling of action-informative neurons and decoupling of non-informative neurons over a longer timescale and across a broader network than typically associated with motor

preparation. These dynamics predicted upcoming action quality and neural activity on individual trials, and performance was impaired when trials were initiated before coupling and decoupling emerged. Two local field potential rhythms organized these dynamics, providing a target for optogenetic intervention that bidirectionally altered action quality. Our work reveals a distributed preparatory process in which selective coupling and decoupling establish a network state that enables skilled action.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

Support: NIH Grant 5R01NS138093-02

Title: Cortically dependent heterogenous signals in the brainstem trigeminal nucleus

Authors: *Y. GAO, B. KARDON, J. H. GOLDBERG;
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Abstract: Accurate goal-directed movements require information about effector position, ongoing motion, and behavioral contexts to be integrated into sensory feedback. Here, with high-speed videography, we examined three-dimensional tongue kinematics as mice re-aimed their licks in response to subtle contact events on the left, center or right part of the tongue. Our electrophysiology recordings in the brainstem trigeminal nucleus (TN) revealed that movement-related signals are integrated with mechanosensory inputs at this lowest level of the central sensory hierarchy. Even more surprisingly, TN represented multiple aspects of task structure, including go cue responses, memory of spout position, and detailed lick cycle information. To investigate the source of such complex modulations, we inactivated the sensorimotor cortices important for orofacial movements (ALM, TJM1, TJS1) during TN recordings. Preliminary findings showed that the cortex may shape TN signals both through gain modulations and by sustaining the persistently divergent signals that encode spout position memory. Our results suggest a cortically dependent mechanism for mixing movement-related and contextual signals at the earliest stage of central somatosensory processing.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

Support: NIH Grant U01 NS136458
McDonnell Center for Systems Neuroscience

Title: Spinal dopamine reports effort levels of motivated locomotion

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Abstract: The spinal cord receives significant descending dopaminergic input from the hypothalamic nucleus, known as A11 in mammals and DC2/4/5 in zebrafish. Pharmacological manipulations in the ex vivo spinal cord have demonstrated that dopamine can generally act via D1-class receptors to increase rhythmic activity, and via D2-class receptors to decrease rhythmic activity. However, the circumstances that elicit dopamine release in the spinal cord, and its spatial extent and targets, are unknown. Here we use dopaminergic reporters (GRAB-DA3m) in the spinal cord of larval zebrafish to examine dopamine release in paralyzed animals. We find that dopamine release in the spinal cord is detectable but minimal during spontaneous locomotion. Similarly, tactile or visual stimuli that do not elicit locomotor responses produce small dopamine transients. However, sensory stimuli that elicit locomotion evoke a large release of dopamine, aligned in time with the beginning of locomotor output. The amplitude of dopamine release was tightly tied to the duration of locomotion, not to other features such as swim frequency. The difference between dopamine release during spontaneous swimming vs sensory-evoked swimming was not due to the duration of locomotion, because even long-duration spontaneous swims did not elicit significant dopamine release. In the temporal domain, dopamine levels ramp up during locomotion, reaching a plateau near the end of locomotion. As a consequence, dopamine reports the integral of locomotor output. Finally, we show that these observations hold generally true regardless of whether GRAB-DA is expressed in excitatory or inhibitory neuron populations in the spinal cord (V2a, V1, V2b), indicating that dopamine release is likely occurring via volume transmission over wide areas. Together these data reveal that dopamine release in the spinal cord reports overall effort levels during sensory-evoked locomotion, suggesting a role in linking sensory signals to motor consequences.

Disclosures: C. Tian: None. **A.D. Douglass:** None. **M.W. Bagnall:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Program #/Poster #: PSTR276.12/EE27

Topic: F.04. Voluntary Movements

Support: ANR-21-NEUC-0001 (BSCLS)

Title: Modular Reticulospinal V2a Control of Natural Turning in Mice

Authors: *A. GIORGI[1], A. LEONARD[1], E. GATIER[1], P. TRAN[2], J. AUSBORN[2], J. BOUVIER[1];
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Abstract: Turning, the ability to change locomotor direction, is essential for animals to navigate their complex environments. Yet, unlike straight-ahead locomotion, its kinematics and neuronal control remain poorly understood, reflecting both the historical lack of tools for 3D tracking and the relatively recent identification of V2a reticulospinal neurons as key drivers for turning. To fill this gap, we adapted a high-resolution motion capture system for mice to dissect the kinematic building blocks of natural turning and to uncover if and how V2a descending pathways are functionally organized to orchestrate the complexity of this behavior. Our 3D analysis of joint-specific rotations and limb stepping dynamics revealed a rich repertoire of natural kinematic strategies for turning, characterized by multiple combinations of asymmetric body-axis configurations, limb-specific gait asymmetries, and precise speed modulation. Strikingly, these three motor macro-components are independently governed by distinct projection-specific V2a reticulospinal modules: V2a>C2-T13 neurons control head-to-tail body-axis alignment, V2a>L1-L4 neurons regulate locomotor speed, and V2a>L5-S2 neurons coordinate left-right gait asymmetries. Altogether, our findings define the core kinematic elements of quadrupedal turning and show that their synergistic deployment during natural behavior relies on a modular V2a reticulospinal architecture, establishing a circuit-level framework for directional locomotor control.

Disclosures: A. Giorgi: None. **A. Leonard:** None. **E. Gatier:** None. **P. Tran:** None. **J. Ausborn:** None. **J. Bouvier:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.13/EE28

Topic: F.04. Voluntary Movements

Support: NIH 1ZIA NS003153

Title: A Spinal Substrate for Modular Control of Natural Behavior

Authors: *F. NICOLA[1,2], L. LI[2], J. E. MARKOWITZ[3], A. LEVINE[2];
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Abstract: Natural behavior unfolds as coordinated sequences of body movements. This organization suggests that behavior may be built from discrete motor patterns, yet how such patterns are implemented by neural circuits remains unknown. Here, we examined the circuit logic underlying natural gap-crossing jumps in mice by combining quantitative kinematic analysis, hindlimb muscle recordings, activity mapping across genetically identified spinal interneuron populations, and closed-loop optogenetic perturbations. Gap-crossing jumps were organized into a series of precisely defined behavioral phases, including preparation, propulsion, flight, and landing. The core phases, propulsion and flight, were defined by distinct hindlimb movement patterns: extension during propulsion and flexion during flight. Across jump distances, these patterns followed different tuning rules, suggesting that natural jumping comprises separable motor elements with distinct control requirements. Closed-loop perturbations further revealed phase-specific needs for spinal neural drive, supporting the idea that different phases of the jump rely on separable neural control mechanisms. To identify cellular substrates for these motor patterns, we mapped activity across lumbar interneuron populations and functionally screened candidate genetically defined cell types for their ability to drive coordinated hindlimb movement. This approach identified a population of dorsal excitatory dILB6 neurons that can autonomously evoke coordinated multi-joint hindlimb flexion, resembling the flight phase of jumping, across behavioral contexts. These findings identify a spinal substrate for a modular component of natural behavior and provide cellular-level evidence that spinal circuits can contribute to discrete, recruitable motor patterns during mammalian action.

Disclosures: F. Nicola: None. **L. Li:** None. **J.E. Markowitz:** None. **A. Levine:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.14/EE29

Topic: F.04. Voluntary Movements

Support: NSF-CRCNS-DARE 2113069
ANR-21-NEUC-0001 (BSCLS)

Title: Simulating locomotor asymmetry and turning-associated phase changes using a computational model of the spinal locomotor CPG

Authors: *P. T. TRAN[1], A. GIORGI[2], A. LEONARD[2], I. AL-SARHANI[1], S. M. DANNER[1], J. BOUVIER[2], J. AUSBORN[1];

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Abstract: Turning is essential for survival in all animals. Yet, unlike straight locomotion, we know little about the neural circuits that mediate limb movements and interlimb coordination during turning behaviors. Observing turning requires freely moving animals, which complicates experimental investigations into the underlying neural mechanisms. Optogenetic stimulations showed that distinct populations of brainstem Gi-V2a neurons projecting to different levels of the spinal cord control distinct aspects of turning. Specifically, unilateral stimulation of cervical-projecting Gi-V2a neurons induces turning ipsilateral to the stimulation, while unilateral stimulation of lumbar-projecting Gi-V2a neurons induces bilateral slowing or stopping (Usseglio et al., 2020). How spinal locomotor CPG circuits transform descending Gi-V2a commands into coordinated turning behaviors remains unknown. We used computational modeling to complement experimental studies. First, we analyzed the experimentally observed turning kinematics and found that all limbs showed an increase in duty factor during turn initiation, but the increase was significantly greater in the inner hindlimb. In addition, we saw an emergence of distinct limb coordination strategies, including 1:N limb patterns. We then tested whether a computational model of the spinal locomotor CPG incorporating bilateral cervical and lumbar rhythm-generating networks and interlimb coordination pathways could generate the kinematic patterns observed during turning. We simulated locomotor asymmetry by unilaterally modifying descending drives to the spinal CPG circuit. Simulations showed that asymmetric descending drive disrupts coordination more readily in hindlimb than forelimb circuits, indicating distinct functional roles for cervical and lumbar networks during turning.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: F.04. Voluntary Movements

Support: A Grant-in-Aid for Scientific Research from MEXT to RY (KAKENHI (B) no. 21H02798)

Title: Chemogenetic inactivation of the PnC-spinal pathway disrupts dexterous grasping in non-human primates

Authors: *Y. SUN[1], R. YAMAGUCHI[1], K. MATSUDA[1], T. ISA[2];
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Abstract: Dexterous finger control is essential for daily life in primates. While the corticospinal tract is well known to regulate individual digit movements, clinical evidence suggests that

additional pathways also play a potential role in hand dexterity. Recent studies suggest that the reticulospinal tract (RST) may contribute significantly to precise hand motor control.In this study, we investigated the specific contribution of the RST to fine motor control in two Japanese macaques (Macaca fuscata) using a two-step loss-of-function approach paired with markerless 3D kinematic tracking. First, we localized acoustic startle response neurons, presumably reticulospinal neurons, in the reticular formation using single-unit recordings. Local microinjection of muscimol functionally mapped the reticular formation and confirmed localized dexterity impairments without other behavioral changes, demonstrating the necessity of the caudal pontine reticular formation (PnC) in manual dexterity. To establish pathway specificity, an intersectional chemogenetic strategy was used by injecting AAV2.1-hSyn-DIO-hM4Di-HA into the unilateral PnC and AAV2retro-CAGGS-Cre into the ipsilateral C7-T1 spinal cord. To quantify behavioral alterations, we developed a DeepLabCut™-based pipeline to reconstruct multi-joint 3D kinematics of the thumb and index finger during natural reach-and-grasp tasks.Systemic administration of deschloroclozapine (DCZ) for pathway-selective inactivation resulted in profound deficits in hand dexterity. While the two monkeys exhibited distinct baseline grasping strategies, RST inactivation significantly reduced grasping success rates, prolonged reaching and grasping durations, decreased movement smoothness, and severely disrupted multi-joint thumb-index coordination, as revealed by dynamic time warping (DTW) analysis in the absence of overt proximal posture deficits. Surface EMG recordings in the forearm revealed disrupted temporal coordination between antagonist flexor and extensor muscle activities. Together, our findings demonstrate that the PnC-spinal pathway is important for fine finger control, specifically by regulating the agonist/antagonist activation pattern and coordination of digit movements rather than maintaining gross proximal stability.

Disclosures: Y. Sun: None. **R. Yamaguchi:** None. **K. Matsuda:** None. **T. Isa:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

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Title: A brainstem substrate for coordinating body, face, and eye movements during orienting

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Abstract: Most motor behaviors can be broken down into “elementary” actions, each involving a restricted set of muscle groups. The brainstem reticular formation (RF) is well-positioned to control such actions at both the spinal (trunk, limbs,⋯) and cranial (orofacial, ocular,⋯) levels. Yet, the specific roles of its diverse neuronal populations remain poorly understood. We recently showed that V2a neurons, a glutamatergic subset in the RF, impose limb and trunk asymmetries, thereby engaging locomotor turning. These actions were attributed to spinal projections of V2a neurons of the gigantocellular nucleus (Gi). We hence question here the possibility that V2a neurons, in the Gi or adjacent regions, stand as a neural controller for multiple orienting-related actions, including at the cranial level. We investigate this by combining, in the mouse, cell-type specific manipulations, connectomics, and optogenetics. First, an efferent connectivity mapping revealed that V2a Gi neurons make abundant synaptic contacts in the brainstem, with the most contacted regions being specific sets of cranial motoneurons. Second, functionally, activating V2a Gi neurons indeed reliably evokes orofacial movements, consistent with sensory apparatus adjustments during orienting. Third, investigating V2a neurons located beyond the Gi revealed that the more rostral ones (pontine RF) can additionally mobilize specific extra-ocular movements, suggesting a rostro-caudal specialization. Fourth, silencing rostral V2a neurons perturbs eye movement during head fixed optokinetic reflex, placing them as an indispensable output pathway for gaze control. These results altogether position V2a reticular neurons and their modular organisation as a key neural orchestrator of multiple components of orienting.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: F.04. Voluntary Movements

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Title: Brainstem coordination of drinking with respiration

Authors: *H. KAKU[1], L. D. LIU[3], R. GAO[2], S. J. WEST[5], S.-M. LIAO[6], A. FINKELSTEIN[8], D. KLEINFELD[7], A. THOMAS[4], K. SVOBODA[9], N. LI[2];
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Abstract: Rhythmic ingestive behaviors such as drinking must be coordinated with breathing to protect the airway while engaging overlapping orofacial musculature. A prevailing model proposes that the respiratory central pattern generator (CPG) acts as a master clock that synchronizes other brainstem motor rhythms. Whether this hierarchy applies when ingestive behaviors directly compete with breathing remains unknown. We examined how breathing, licking, and swallowing are coordinated during naturalistic drinking in mice. Orofacial movements were tracked with high-speed videography, breathing was measured with an airflow sensor, and swallowing was detected using X-ray videofluoroscopy. Licking and breathing were tightly phase-locked, while intermittent swallowing transiently suppressed both, indicating that ingestive behaviors actively regulate breathing. To identify the brainstem circuits coordinating these orofacial rhythms, we performed brainstem-wide recordings using Neuropixels probes. We identified distinct neural populations modulated by breathing, licking, or swallowing, including a region in the intermediate reticular nucleus (IRN) with rhythm-generation properties sufficient to drive sustained licking, consistent with a licking central pattern generator. Simultaneous recordings from the IRN licking region and preBötzinger complex (preBötC) revealed reciprocal circuit-level coupling between licking and breathing rhythm-generating centers. Causal manipulations further demonstrated bidirectional coupling: inhibition of the IRN licking region disrupted licking but also paused breathing, whereas inhibition of the preBötC suppressed both breathing and ongoing licking. Conversely, activation of the IRN licking region entrained breathing, enabling self-organized coordination of licking-breathing without hierarchical control. In contrast, swallowing was functionally upstream of both licking and breathing oscillators. Swallowing was triggered by oral water accumulation, independently of licking, and acted unidirectionally to suppress both licking and breathing oscillators. Together, these results provide a circuit-level account of how competing ingestive and respiratory rhythms are coordinated to ensure safe drinking. Our findings support a coupled-oscillator framework in which interacting brainstem CPGs self-organize competing motor programs for shared motor and airway resources, rather than top-down synchronization.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

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Program #/Poster #: PSTR276.19/FF2

Topic: F.04. Voluntary Movements

Support: NIH Grant U01NS136458-01

Title: Roles for descending dopaminergic modulation of defensive behavior in larval zebrafish

Authors: *S. N. BROCKWAY, A. D. DOUGLASS;
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Abstract: Dopamine (DA) is a neuromodulator known to influence animal behavior through its involvement in reinforcement learning and internal state regulation across vertebrate species. Descending avenues by which DA may modulate sensory processing and motor behavior via projections to the hindbrain and spinal cord are less understood. Two-photon imaging of calcium and dopamine sensors expressed in behaving larval zebrafish showed that th1 neurons in the posterior tuberculum, which synthesize DA and send their axons to the spinal cord, are active during escape behavior elicited by an artificial nociceptive stimulus. Interesting, the same correlation is not observed during spontaneous escape behavior. In the dorsal spinal cord, DA release increases upon delivery of a nociceptive stimulus, with the amount of DA release varying even among neurons closely located within the cord. Together, these results suggest that spatially and temporally precise DA release to spinal sensory circuits may play an important role in modulating vertebrate behavior in response to a changing sensory environment.

Disclosures: S.N. Brockway: None. **A.D. Douglass:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.20/FF3

Topic: F.04. Voluntary Movements

Title: Automating Reach-to-Grasp Behavioral Analysis with LabGym

Authors: *T. FRIEDLANDER[1], D. K. LEVENTHAL[2,3];
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Abstract: The reach-to-grasp task is used in basic and translational research to model motor learning and dexterous motor control. To correlate neural signals with behavior or determine the effects of neural perturbations on reaching, we need to segment videos into specific reach phases. This can be accomplished manually, but this is time-consuming and labor-intensive. An automated process would significantly improve video processing speed and enable thousands of

videos to be analyzed with minimal human supervision. We used the machine learning package LabGym to segment high-speed videos of rat reach-to-grasp. LabGym allows users to train a detector to identify objects of interest. After segmenting videos into small intervals, users distinguish the object's behaviors to train a 'categorizer' that identifies movement patterns associated with the defined behaviors. I used front-facing videos from the reach-to-grasp task in a pellet-pedestal rodent apparatus. We trained a detector to reliably identify the rat and sugar pellet used in the reach-to-grasp task. We identified 3 'behaviors' for the pellet and 12 for the rat- 2 generalized behaviors, 5 reach-specific behaviors for the left paw, and 5-reach specific behaviors for the right paw. We quantified performance using the F1 score and comparison with 10 manually segmented videos. The F1 score measures classification accuracy, and ranges from 0.0 to 1.0 with 1.0 being a perfect model. The F1 score for the categorizer was 0.8, which is considered a good balance between precision and recall. The comparison to 10 manually annotated videos reveals consistency for common behavioral features like pellet consumption or rat approaching the pedestal, but LabGym is less accurate for fine behaviors such as grasping or paw retraction. The largest model discrepancy is in identifying the left and right paws. In addition to accurately identifying behaviors, the segmentation agreed with manual curation to about 0.1 s precision. LabGym is a promising approach to automatically identify reach-to-grasp behaviors, but requires further refinement to identify more subtle movements.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Program #/Poster #: PSTR276.21/FF4

Topic: F.04. Voluntary Movements

Support: NSF EAGER 2124608
NSF CAREER 2338662

Title: Measuring the contributions of model-driven feedforward control and sensory-driven feedback control to movement in non-human primates

Authors: *K. M. PERKS[1], L. I. SMITH[2], S. A. BURDEN[2], A. L. ORSBORN[2];
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Abstract: To control a motor effector (e.g. a limb or computer mouse), we rely on sensory information from the environment (*feedback control*) and internal models about the way the effector works (*feedforward control*). The brain is hypothesized to use feedforward and feedback control together to generate precise, flexible movements, yet the field lacks methods to simultaneously measure the contributions of each controller to behavior. Without such a method, it is difficult to understand how feedforward and feedback computations shape behavior nor their implementation in neural circuits. Human psychophysics paradigms used to probe internal

models are insufficient because they rely on removing or clamping feedback signals to isolate model-driven feedforward control, which does not capture how both forms of control contribute to movements in real life. Continuous tracking paradigms have been used to disentangle feedforward and feedback control, but have not been developed for animal models commonly used for detailed neurophysiology. Here, we develop and validate a control theoretic tracking task in monkeys. We trained two male rhesus macaques to control the movement of a 1D cursor using unconstrained 3D hand movements. We specified a mapping that transformed their hand position into an intended cursor position, or *user response*. The monkeys used this mapping to perform a 1D tracking task, which consisted of following a continuously moving reference signal while also correcting for a disturbance signal continuously applied to the user response. This task is built on a control theoretic framework that models the user response as a combination of feedforward control acting on the reference and feedback control acting on the error between the reference and cursor. Estimating the two controllers in this framework relies on modeling the user as a linear time-invariant (LTI) system and constructing the reference and disturbance from distinct sets of frequencies to create two independent signals that the user responds to. After training, both monkeys excelled at the task and made movements well-aligned to the mapping. We found the LTI assumption of the task framework holds in a monkey model. Their measured controllers had distinct frequency-domain profiles, with the feedforward controller revealing anticipatory, gain-matched responses to the reference signal and the feedback controller revealing reactive, frequency-dependent responses to the error signal. Our results offer novel insights into how the two forms of control contribute to movement in monkeys and establish new methods for future studies into the neural mechanisms underlying feedforward and feedback control.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Program #/Poster #: PSTR276.22/FF5

Topic: F.04. Voluntary Movements

Support: DARPA Cooperative Agreement Number W911NF-24-2-0112
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Title: Metabolic-Modulating Compounds as a Novel Class of Anesthetics

Authors: *H. FOTOWAT, K. SHEEHAN, A. GABROS, T. LIN, A. PAUER, M. M. SPERRY, D. E. INGBER;
Wyss Inst. at Harvard Univ., Boston, MA

Abstract: General anesthesia currently requires elaborate instrumentation and highly trained medical personnel because these drugs abolish the central nervous system's ability to regulate involuntary physiologic processes such as respiration, thermoregulation, and heart rate. There is a pressing need for alternative strategies that would permit safe medical care in settings where such equipment and expertise are not available, including battlefields and disaster zones. In this study, we sought to address this need by chemically inducing a torpor-like state. Torpor is a natural behavioral state characterized by a regulated reduction in metabolism and reversible suppression of neural activity that, like general anesthesia, produces immobility and unresponsiveness to sensory stimulation. In contrast to existing anesthetics, however, vital autonomic functions (e.g., heart rate and respiration) remain under internal control during torpor. We previously identified the existing drug SNC80, a δ-opioid receptor (DOR) agonist, and developed novel variants in which DOR activity is reduced ~1000-fold. These metabolic-modulating compounds (MMCs) rapidly and reversibly slow metabolism at the cellular, tissue, and organ levels and suppress swimming in *Xenopus* tadpoles, mimicking a torpor-like state. Here we report that, in addition to suppressing movement, these MMCs markedly reduce responses to sensory and noxious stimuli, matching or exceeding the performance of state-of-the-art anesthetics such as propofol, etomidate, and ketamine. Tadpoles treated with the lead MMC, WB3, fully recover mobility and responsiveness to sensory and painful stimuli, as well as simple forms of learning (habituation), after washout. Interestingly, when combined with anesthetics and sedatives that act on the GABAergic pathway (propofol, etomidate, and benzodiazepines), WB3 exhibits strong synergy, suggesting action on overlapping or convergent mechanisms. Together, these findings identify a promising alternative to conventional anesthesia with potential for safer, resource-limited clinical applications.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

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Topic: F.04. Voluntary Movements

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Title: Neurophysiological characterization of a pharmacologically-induced hypometabolic state by a novel designer drug

Authors: *F. J. FLORES[1,2,3], Q. TRAN-PEREZ[4], H. FOTOWAT[5], M. A. WILSON[1], D. E. INGBER[5], E. N. BROWN[1,2,3];
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Med. Sch., Boston, MA; [4]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [5]Wyss Inst. for Biologically Inspired Engin., Harvard Univ., Boston, MA

Abstract: Natural hypometabolic states like torpor and hibernation have profoundly affect brain activity, yet brain function fully recovers after these states end. Achieving a similar hypometabolic state safely and reversibly with pharmacological means would allow non-hibernating animals to obtain the same benefits under traumatic or challenging conditions. SNC80 is a strong metabolic modulator originally developed as a non-addictive analgesic, but its action on the δ-opioid receptors (DOR) caused seizures as side effects in pre-clinical studies that precluded its clinical use. To preserve the metabolic-modulating effects while eliminating DOR-related side effects, a novel SNC80 analog, WB3, with a ~1000-fold reduction in DOR-binding activity was developed and found to result in metabolic suppression and immobility in *Xenopus*. However, the effects of WB3 on the neurophysiological activity of vertebrates remain unknown. To test this, we administered different doses of WB3 to freely-moving mice while recording electroencephalography (EEG), electromyography (EMG) and behavior. We found that WB3 produces a fast and dose-dependent reduction in body temperature, EEG power, and locomotor activity. These effects are reversible, with dose-dependent recovery time. Notably, WB3 did not produce a rapid, sustained increase in δ power (1 - 4 Hz) typically observed in sedative and anesthetics drugs, but the overall decrease in EEG power resembles what is reported during torpor, consistent with its expected hypometabolic properties. Unexpectedly, WB3 at higher doses also produces short but well-defined spindle-like oscillations around 6 Hz. We observed similar oscillations following administration of dexmedetomidine, a sedative that slows brain metabolism, and ketamine, an anesthetic and psychotomimetic that maintains or even increases metabolic rate. Our results strongly suggest that most of the effects of WB3 on brain activity and behavior are related to its hypometabolic action, but the presence of spindle-like oscillations also suggests involvement of the thalamocortical system and the potential of WB3 to modulate consciousness states independent of its hypometabolic effects.

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Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

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Program #/Poster #: PSTR276.24/FF7

Topic: F.04. Voluntary Movements

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NIH Grant DP2-MH1194025

Title: A dopamine DART toolset for acute, cell-specific pharmacology

Authors: B. C. SHIELDS[1], S. YOUSEFZADEH[2], H. YAN[4], Z. FARAHBAKHSH[3], M. MCDONNELL[5], A. REITZ[5], ***M. R. TADROSS**[3];
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Abstract: Dopamine acts through multiple receptor classes to modulate neural circuit function, but conventional pharmacology cannot easily resolve which receptor actions occur in which cell types. We are developing a dopamine DART (Drug Acutely Restricted by Tethering) toolset to enable acute, genetically targeted manipulation of dopamine receptors. In this approach, HaloTag Protein expressed on selected cells captures a HaloTag-ligand drug conjugate, locally enriching the pharmacological payload at defined cell surfaces while limiting ambient drug exposure.
Our current dopamine DART panel includes four complementary reagents: a D1 antagonist, SCH23390.7-DART.2; a D1 agonist, SKF38393.1-DART.2; a D2 antagonist, L741626.3-DART.2; and a D2 agonist, sumanirole.2-DART.2. Development of the D1 antagonist illustrates the design strategy. Initial SCH23390 derivatives showed poor D1R activity, prompting structure-guided redesign of the linker attachment site on the unfused phenyl ring. Subsequent PEG-linked analogs were screened in D1R and D2R Tango GPCR assays, identifying SCH23390.7-PEG as a selective and appropriately tuned D1R antagonist lead for conversion into SCH23390.7-DART.2.
Together, these reagents provide bidirectional control over D1- and D2-class dopamine receptor signaling with cell-type specificity. This toolset will enable direct tests of how dopamine receptor activation or blockade in defined neuronal populations shapes circuit dynamics and behavior, including ongoing studies of dopaminergic modulation of spinal locomotor circuits in vivo.

Disclosures: B.C. Shields: None. **S. Yousefzadeh:** None. **H. Yan:** None. **Z. Farahbakhsh:** None. **M. McDonnell:** None. **A. Reitz:** None. **M.R. Tadross:** None.

Poster

PSTR276: Action/Sensation/Movement Selection: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR276.25/FF8

Topic: A.07. Development of Neural Systems

Support: NIH Grant R01 EY033845

Title: Modeling Behavioral Stability During Neural Circuit Development

Authors: *C. FEHRMAN, J. MORRA, E. A. NAUMANN;
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Abstract: Nervous systems maintain functional behavior despite continual changes in neural circuit structure, body morphology, and sensory-motor relationships during development. To investigate how stable behavior emerges despite ongoing developmental changes in neural circuits and body structure, we developed a computational framework for neural and behavioral development inspired by the larval zebrafish optomotor response (OMR). Simulated agents interacted with moving visual grating stimuli while neural circuit size, neuron number, and sensory geometry changed over developmental time. Neural connectivity was generated using a HyperNEAT-based developmental encoding in which a Compositional Pattern Producing Network (CPPN) mapped neuron spatial coordinates and developmental time to connection weights. This produced a distinct connectome at each developmental stage from a shared set of generative rules, allowing neurogenesis and circuit growth without altering the learned CPPN. CPPNs were optimized via evolutionary search to produce embodied agents that perform OMR across a set of discrete developmental stages. Despite optimization only at these stages, evolved controllers generalized to intermediate developmental time points not encountered during training. OMR performance, quantified by the distribution of turn angles during swim bouts, remained stable throughout development even as circuit size, neuron number, and sensory geometry changed substantially. These results demonstrate that a single developmental encoding can generate functionally stable behavior despite continual changes in the neural circuits that produce it. Our findings suggest that stable behavior can emerge from shared developmental rules rather than fixed neural architectures, providing a computational framework for investigating how neural representations reorganize throughout growth while preserving function.

Disclosures: C. Fehrman: None. **J. Morra:** None. **E.A. Naumann:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.01/FF9

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS118197 to H.L.

Title: Motor training stabilizes dynamic speed tuning in layer 2/3 neurons of the primary motor cortex

Authors: *S. BETTS MENDIZABAL[1], Y. YUE[1], J. YUAN[2], C. ASH[2], G. YUAN[2], C. ZENG[1], H. LU[1];
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Abstract: Repeated training drives motor skill acquisition and adaptive refinement of movement. The primary motor cortex (M1) plays a necessary role in these functions with crucial contributions from layer 2/3 (L2/3) neurons, yet how M1 population activity evolves during training to improve locomotor accuracy and efficiency remains incompletely understood. To address this question, we trained mice on a computer-controlled treadmill with variable speeds for 12-14 days while performing chronic in vivo two-photon calcium imaging of M1 L2/3 neurons. Mice improved gait kinematics, reflected by fewer strides and more reliable paw-position distributions after the early learning phase. At the population level, the average calcium event rate separated rest from running but did not distinguish the four running speeds. In contrast, individual L2/3 neurons showed diverse speed tuning: more than 60% were speed-tuned, including neurons whose event rate increased at a preferred speed, decreased at a preferred speed, or changed linearly with speed. Speed tuning was initially dynamic across days. With training, however, the proportion of coding-stable neurons increased from about 22% during the early learning phase to about 31% during consolidation, and the increase in coding stability correlated with behavioral improvement. Functional connectivity, estimated from pairwise correlations, also strengthened preferentially among actively speed-coding neurons, suggesting training-dependent refinement of a task-relevant ensemble. Principal component analysis of the same neurons tracked across days showed that running-related population trajectories expanded early in training and converged during consolidation, whereas rest-related trajectories did not show the same pattern. Consistent with this stabilization, cross-day machine-learning prediction of treadmill speed from population activity improved with training. These results indicate that M1 L2/3 neurons encode locomotion speed through distributed, initially flexible activity patterns that become more stable as animals acquire adaptive locomotor skill. Motor training may therefore improve performance by reducing variability in cortical kinematic representations and strengthening connectivity among speed-responsive ensembles.

Disclosures: S. Betts Mendizabal: None. **Y. Yue:** None. **J. Yuan:** None. **C. Ash:** None. **G. Yuan:** None. **C. Zeng:** None. **H. Lu:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.02/FF10

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI grant numbers 16K01490
JSPS KAKENHI grant numbers 21H06448
JSPS KAKENHI grant numbers 24K09702

Title: Information flow of motor and apparent error signals through cortical, rubral, and cerebellar circuits during reaching

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Abstract: Trial-by-trial adaptation of reaching is driven by error information that can be decomposed into at least two components: motor error (ME), estimated from ongoing motor commands and proprioceptive feedback, and visual apparent error (AE), the discrepancy between target and touch positions. Previous studies in macaques showed that cerebellar climbing fibers and neurons in M1, premotor cortex (PM), parietal area 5, and the parvocellular and magnocellular red nucleus (RNp and RNm) encode error-related information, and that stimulation of M1, PM, area 5, and RNp, but not RNm, can drive adaptive changes in reaching (Kitazawa et al., 1998; Inoue et al., 2016; Inoue and Kitazawa, 2018, 2025). However, the temporal order and direction of information flow for ME and AE across cerebral cortex, RNp, RNm, and the cerebellum have not been directly compared.We reanalyzed macaque single-unit datasets obtained in closely matched rapid-reaching tasks (M1, n=157; PM, n=80; area 5, n=161; RNp, n=123; RNm, n=72; cerebellar complex spikes, n=50 Purkinje cells), and estimated the onset latency of ME- and AE-related information using mutual information analysis aligned to movement and feedback events. AE-related information appeared first in cortical areas, including M1 (median = 170ms, n = 57), PM (140ms, n = 24), and area 5 (170ms, n = 56), and later in RNp (220ms, n = 36), RNm (280ms, n = 19), and cerebellar complex spikes. By contrast, ME-related information emerged earliest in RNp (median = 170ms, n = 37) and RNm (180ms, n = 28) during movement, preceding its appearance in cortical areas (M1, 280ms, n = 68; PM, 295ms, n = 24; area 5, 300ms, n = 62) and in cerebellar complex spikes.Together, these opposite temporal gradients suggest two partially distinct but interacting routes of error-information flow. Visual AE appears to arise first in cortical areas and then pass through RNp to the inferior olive and cerebellar climbing fibers, providing a teaching signal for trial-by-trial adaptation. In contrast, ME emerges first in RNp and RNm during the movement, consistent with a predictive error signal derived from cerebellar nuclear output. RNp is therefore positioned to integrate cortical AE with cerebellar predictive ME and relay the combined error information to the inferior olive, whereas RNm may use early ME signals, together with cortical motor pathways, for online correction of ongoing reaching movements.

Disclosures: M. Inoue: None. **S. Kitazawa:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.03/FF11

Topic: F.04. Voluntary Movements

Support: NIH R01 DC018691

Title: Operant Training of Mouse Ultrasonic Vocalizations

Authors: *E. LUO[1], C. D. VARGAS[2], H. RIVERA BERMUDEZ[3], E. D. JARVIS[1];
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Abstract: Sparse projections from the mouse primary motor cortex (M1) to brainstem vocal motor neurons suggest that mice may have the anatomy necessary for a limited level of vocal learning. We aimed to test the behavioral capacity of mice to perform **vocal usage learning**—the ability to use innate or acquired vocalizations in novel behavioral contexts. We hypothesized that C57Bl6 mice can learn to increase their rates of ultrasonic vocalizations (USVs) in an operant training paradigm that delivered positive reinforcement for any USVs. We designed a home-cage operant conditioning Feeding Experiment Device (FED) that dispenses a sugar pellet reward when a USV is detected. Over the course of 2-3 weeks, experimental male mice were housed individually in a free-behaving environment with the FED, and monitored and rewarded continuously for vocalizations. A yoked control mouse, housed in a separate individual cage, was simultaneously monitored for any vocalizations, but received sugar pellet rewards linked to the experimental mouse's USVs, not its own. We measured daily USV production to assess the extent of vocal usage learning. The FED was capable of dispensing a sugar pellet in a sub-second interval between USV detection and reward, but mice that were reinforced for their vocalizations did not learn to increase their USVs compared to their yoked-control counterparts. We will continue using the FED operant conditioning paradigm to assess the vocal learning abilities of wild type, transgenic, and humanized mice, which will provide insight into the specific genes and circuits that support our own advanced vocalization behavior.

Disclosures: E. Luo: A. Employment/Salary (full or part-time):; The Rockefeller University. **C.D. Vargas:** None. **H. Rivera Bermudez:** None. **E.D. Jarvis:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.04/FF12

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS117749

Title: The role of the lateral reticular nucleus in forelimb motor control and learning

Authors: *J. D. ROSS[1], G. T. KOMA[2], A. J. SPENCE[2], G. M. SMITH[3];
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[2]Bioengineering, [3]Dept of Neurosci., Temple Univ., Philadelphia, PA

Abstract: Motor rehabilitation depends on our capacity to modify motor control circuits. Although the cortico-pontine-cerebellar tract is known to generate motor blueprints, its inefficiency stemming from sensory latency requires faster adjustments. Evolutionary demands produced a mechanism capable of instantaneous movement correction. This setup employs a forward model where an efferent duplicate of motor instructions transforms into sensory forecasts to be evaluated against incoming feedback. This efferent duplicate travels to the cerebellum through the lateral reticular nucleus (LRN), accelerating motor adaptation. Situated in the medulla, the LRN is thought to orchestrate intricate forelimb actions, though its precise role remains unclear. Our findings show that the LRN synthesizes and transmits motor signals to preserve forelimb accuracy, demonstrating that the spinal-LRN-cerebellar route is crucial for sharpening expert motor sequences and recovery.
To explore the function of the LRN, we engineered a vGlut1-Cre Long Evans rat model to selectively isolate vGlut1 neurons within the LRN via the Cre-lox mechanism. We generated AAV vectors, such as AAV8-mCherry-flex-dtA, which eliminates LRN neurons post-injection without damaging surrounding tissue. We evaluated three cohorts: one without prior training before dtA ablation, one with advance training before ablation, and one untrained prior to injection of an inhibitory DREADD, namely hM4Di. Within each category, half the subjects obtained the ablating vector and the remaining half received a control vector.
Regarding the untrained cohort (n=10), ablating the LRN obstructed the mastery of the skilled reaching exercise, causing success metrics to drop substantially. Already-trained rats (n=12) displayed an incomplete restoration of capabilities following the procedure, demonstrating that the LRN also matters for preserving learned skills. Ablated subjects in this category flattened out at a 60% success mark, whereas control subjects rebounded to 80%. In the DREADDs cohort (n=10), DREADDs subjects proved unable to learn the behavior in contrast to the controls, emphasizing the LRN's importance in initial motor learning. Every ablated rat displayed kinematic flaws such as overextending. We deduce that the LRN is vital for initial learning of skilled motor tasks as well as the preservation of those abilities in the lifetime of the animal. Our current investigations employing DREADDs examine the LRN's short-term and long-term roles in motor learning and performance by temporarily silencing it, while also assessing its involvement in adapting to real-time disruptions during motor exercises.

Disclosures: J.D. Ross: None. **G.T. Koma:** None. **A.J. Spence:** None. **G.M. Smith:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.05/FF13

Topic: F.04. Voluntary Movements

Support: NIH Grant IK2RX004558

Title: Cell-type-specific inhibition supports the sequential activation of preparatory ensembles in secondary motor cortex

Authors: *B. BAUBLYTE, C. LU, F. APARICIO, K. GANGULY, S. ARROYO;
Neurol., UCSF, San Francisco, CA

Abstract: How distinct cell types contribute to the appearance and coordination of preparatory dynamics in frontal motor cortices during learning remains unclear. In this study, we use high-density silicon probe recordings with optotagging to investigate the development of preparatory activity patterns in SST and PV interneurons, as well as pyramidal neurons, in M2, over learning of cued lever-press task in mice. We find that some move-related pyramidal neuron ensembles present early in learning gradually shift their selectivity to cue, splitting preparatory excitatory population activity into cue- and move-related components, and paralleling behavioral learning. A tuning shift is also observed in single PV interneuron activity, which becomes increasingly modulated by cue as early as the respective shift occurs in the pyramidal cue-related ensemble. In contrast, task-modulation of SST interneurons is delayed and resultant patterns are more varied: single SST interneurons exhibit tuning to either cue or movement, or both. Overall, SST population displays greater activity during move onset, overlapping with the moment of hand-off from excitatory cue- to move-related ensemble activity, implicating SST interneurons in the coordination of preparatory dynamics in the learned state. Our next steps will aim to relate the cell-type specific preparatory patterns in wake to task-related reactivations in sleep, to further delineate the role of cell-type specific inhibition to the emergence of robust dynamics during learning.

Disclosures: B. Baublyte: None. **C. Lu:** None. **F. Aparicio:** None. **K. Ganguly:** None. **S. Arroyo:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.06/FF14

Topic: F.04. Voluntary Movements

Title: A Bayesian model of learning and decision making in the anterolateral motor cortex and the basal ganglia

Authors: *T. KOÓS[1], M. E. LIBERADOR DOS SANTOS NUNES[2];
[1]George Mason Univ., Fairfax, MD; [2]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Hoboken, NJ

Abstract: Discrete attractor dynamics in the antero-lateral motor (ALM) cortex in rodents computes choice decisions and maintain working memory in cued-choice tasks. Based on the serial dependence of behavioral choice and neuronal responses in an auditory cued 2-choice task, we propose a Bayesian model of the ALM's functioning and its interaction with the basal ganglia. At cue onset, associatively learned connectivity between cue (C) representations and the ALM, as well as local interactions representing trial history, set the network’s dynamic state (S),

representing the context-dependent, learned behavioral interpretation of the input. The probability of entering one of *n* states after a cue is the prior probability, *p(Sn|C)*. Each learned action corresponds to a stable learned attractor state in the ALM. The likelihood that one of *k* rewarded actions, *Rk*, is given to a cue in state, *p(Rk|Sn)*, is determined by the probability of the network transitioning from *Sn* to *Rk,* which is a function of its initial state, learned feedback connection weights among ALM neurons, and network noise. Feedback connections among ALM neurons are updated by a Hebbian rule. ALM attractor states require positive feedback interactions via thalamocortical connections, which is gated by shunting inhibition from the BG. We suggest that the disinhibitory effect of the BG is learned from dopaminergic reinforcement having a magnitude that is proportional to the marginal likelihood (overall reward probability) because the learning of response-selective BG responses is slower than the development of discriminative attractor states in the ALM.Consequently, the effect of the BG shunting inhibition is to divisively scale the Hebbian update of the positive feedback (and cue to ALM connections) in the ALM, which means that the update of the feedback connections is proportional to the posterior probability (i.e., that the network was in *Sn* prior to transitioning to *Rk*). The model is formally consistent with transitioning from goal-directed to habitual control of behavior, provides a unified mechanism in which the individual stimulus-response likelihoods and decision making are performed by the same system, and predicts serial dependence as a trial-to-trial update of feedback connections in the ALM.

Disclosures: T. Koós: None. **M.E. Liberador Dos Santos Nunes:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.07/FF15

Topic: F.04. Voluntary Movements

Title: Temporal Dynamics of Reaching Kinematics and Error Profiling Reveal Disrupted Motor Skill Consolidation in a Mouse Model of Rett Syndrome

Authors: *M. MAHROUS[1], F. WEBB[2], J. ZHANG[2], E. WADE[5], B. Y. LAU[3], K. KRISHNAN[4];
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Abstract: Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations in MECP2 and is characterized by severe motor dysfunction. While prior studies have characterized reduced motor performance in Mecp2 mutants, it remains unclear whether these deficits arise from impaired acquisition of motor skills or a failure to refine movement execution. In this study, we tracked the day-by-day progression of fine motor skill learning in female C57BL/6J wild-type (WT, n = 13) and Mecp2 heterozygous (Het, n = 12) mice (10-12 weeks old) trained

on a single-pellet reach-to-grasp paradigm over 16 consecutive days. Utilizing DeepLabCut and BORIS, we tracked mice hands to map reaching trajectories and profiled behavioral outcomes across ~24,000 reaches. Statistical differences were assessed using linear mixed-effects models, ANOVA, segmented piecewise regression, and post-hoc tests (alpha=0.05). WT mice exhibited a highly dynamic, three-phase learning trajectory: an early exploratory phase characterized by high trajectory variability and low success rates, a mid-training optimization phase with rising success rates, and a late consolidated phase defined by highly stereotyped, linear trajectories and a dramatic reduction in errors. In contrast, Mecp2 Het mice demonstrated an intact capacity for early behavioral modification but showed a severe, specific deficit in transitioning from exploration to consolidation. Across the 16 days, Het mice maintained persistent trajectory variability, shorter and slower reaches, and randomized trajectories that failed to develop WT expert-level stereotypes. Furthermore, day-by-day profiling revealed that WT mice shifted from inefficient multi-reach trials to refined single-reach bouts, transitioning from proximal targeting errors to fine distal manipulation errors. Alternatively, Het mice failed to undergo error-based updating; they persistently relied on multi-reach trials, could not overcome proximal trajectory errors for longer days, and displayed an elevated rate of impulsive phantom reaching, indicating deficits in sensory gating and inhibitory control. Together, these findings demonstrate that Mecp2 deficiency specifically disrupts the kinematic refinement, temporal consolidation, and multisensory gating required for expert-level motor skill acquisition.

Disclosures: M. Mahrous: None. **F. Webb:** None. **J. Zhang:** None. **E. Wade:** None. **B.Y. Lau:** None. **K. Krishnan:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.08/FF16

Topic: F.04. Voluntary Movements

Support: NIH Training Grant NINDS T32 NS086749
NIH Grant R90DA060340-02S1

Title: Automaticity and motor learning: changes in spinal activity and cortical activation during split-belt adaptation

Authors: *C. ROCK[1], S. LIU[2], N. W. BRANTLY[2], D. J. WEBER[3], A. K. THOMPSON[5], H. GEYER[4], G. TORRES-OVIEDO[2];
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Abstract: Motor learning, which is crucial for neurorehabilitation, is highly heterogenous and the sources of this heterogeneity are unknown. One potential source is a person's degree of gait

automaticity, with high automaticity defined by primarily spinal control of gait with little involvement of attentional control. However, the neural determinants of automaticity have not been comprehensively assessed during motor learning. Therefore, the goal of this project is to assess gait automaticity by simultaneously quantifying spinal reflex activity and cortical activation during motor learning. Our central hypothesis is that automaticity is linked to motor learning, such that a person's degree of automaticity increases as motor learning progresses. METHODS: As a preliminary test of this hypothesis, we recruited 3 participants (Age: 22.3 ± 1.2 years; 2M/1F) to assess automaticity during split-belt walking - a well-established paradigm for inducing motor learning, where participants walk with each leg moving at different speeds. Motor learning was assessed via step length asymmetry. Automaticity was assessed via two measures: H-reflex amplitude - a reliable measure of spinal excitability - and prefrontal cortex activity via functional near-infrared spectroscopy - an indirect measure of attention-related neural activity. RESULTS: Participants all exhibited strong adaptation to the split-belt paradigm, characterized by a reduction in their step-length asymmetry over the adaptation period (Early Adaptation -0.12 ± 0.05; Late Adaptation -0.05 ± 0.04). Concurrently, automaticity was reduced in early adaptation, with initially low spinal reflex excitability (H-reflex: 29 ± 23 μV) and high prefrontal cortex activity (3.19 ± 1.50 above baseline; t-score), followed by increased automaticity by the end of adaptation, with increased spinal activity (H-reflex: 70 ± 16 μV) and reduced prefrontal cortex activity (1.23 ± 1.33 above baseline). CONCLUSIONS: Consistent with our hypothesis, automaticity increased as motor learning progressed, indicating an interdependence between automaticity and motor learning. By linking neural mechanisms to motor learning, this project will provide a mechanistic understanding of motor learning that can be leveraged to improve neurorehabilitation.

Disclosures: C. Rock: None. **S. Liu:** None. **N.W. Brantly:** None. **D.J. Weber:** None. **A.K. Thompson:** None. **H. Geyer:** None. **G. Torres-Oviedo:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.09/FF17

Topic: F.04. Voluntary Movements

Support: AHA Fellowship 25POST1371882

Title: The striatum coordinates cortical and brainstem activity during reach learning

Authors: *C. L. WOODARD, K. GANGULY;
Neurol., UCSF, San Francisco, CA

Abstract: Learning a new motor skill engages a network of cortical and subcortical regions, including motor cortex, the basal ganglia, and thalamus. While plasticity in the cortical-basal ganglia-thalamic loop is known to be necessary for skill learning, it's less clear how it shapes

activity in downstream motor centers involved in generating the motor output. One possibility is that cortex directs descending control throughout learning, with the rest of the loop serving primarily to refine cortical output to the brainstem and spinal cord. An alternative is that learning reallocates control toward subcortical routes, with the striatum increasingly engaging brainstem motor regions through basal ganglia output pathways. To distinguish these possibilities, we recorded simultaneously from primary motor cortex (M1), dorsolateral striatum (DLS), and the medullary reticular formation (MedRF) as mice learned a skilled reaching task requiring precise spatial targeting. Learning was accompanied by a marked increase in coordinated pre-movement activity across all three regions, with MedRF becoming progressively integrated into the network as reach targeting improved. Critically, this integration was neither purely cortical nor cortex-independent; instead, the DLS acted as a hub linking cortical and brainstem preparatory dynamics. Cortico-brainstem coordination depended on the striatum, and disrupting DLS impaired both cortico-brainstem coordination and reach accuracy. These results show that the striatum's contribution to motor learning extends beyond the recurrent cortico-basal ganglia-thalamic loop: rather than the cortex commanding the brainstem directly or the striatum bypassing it, DLS becomes the coordinator that recruits brainstem motor centers into a distributed network during skill learning.

Disclosures: C.L. Woodard: None. **K. Ganguly:** None.

Poster

PSTR277: Motor Learning: Animal (Behavior/Physiology/Imaging)

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR277.10/FF18

Topic: F.04. Voluntary Movements

Support: NIH Grant R01DA054583
NIH Grant 1R01NS118030-01A1

Title: Motor cortical opioid signaling modulates termination of skilled behavior

Authors: *Y. QIU[1], J. NIEHAUS[2], A. W. HANTMAN[3], G. SCHERRER[4];
[1]UNC Neurosci. Ctr., UNC - Chapel Hill, Chapel Hill, NC; [2]Neurosci. Ctr., Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [3]Cell Biol. and Physiology, Neurosci. Ctr., UNC-CH, RCP, Chapel Hill, NC; [4]UNC Neurosci. Center, Dept of Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: The functional scope of the opioid system has been historically restricted to nociception and reward processing, obscuring the fundamental purpose of its widespread distribution across the nervous system. Specifically, in the cerebral cortex, although opioid peptides and receptors are known to be expressed by multiple types of neurons, the precise mechanisms and functional consequences of cortical opioid neuromodulation remain elusive. To address this question, we investigated opioidergic neuromodulation in the mouse primary motor

cortex using a skilled reach-to-grasp behavior, with a specific focus on *Penk*-expressing (*Penk*+) neurons and enkephalinergic signaling. Using two-photon calcium imaging and in vivo electrophysiology, we isolated distinct termination-aligned activity in both *Penk*+ neurons as well as in the broader M1 population. Furthermore, pharmacological blockade of local opioid receptors and optogenetic manipulation of *Penk*+ neurons altered behavioral termination. Collectively, this study extends the canonical view of the opioid system, establishing a critical role of the cortical opioid system in orchestrating motor task termination.

Disclosures: Y. Qiu: None. **J. Niehaus:** None. **A.W. Hantman:** None. **G. Scherrer:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.01/FF19

Topic: G.03. Stress and the Brain

Support: NIH Intramural Grant
NIH CCB Postdoctoral Fellowship

Title: Microglial GPR110 modulates inflammation-associated behavioral outcomes

Authors: *M. MELKUMYAN, B. X. HUANG, H.-Y. KIM, D. M. LOVINGER;
NIH, Rockville, MD

Abstract: GPR110 (ADGRF1) is an adhesion G protein-coupled receptor involved in neurogenesis, synaptogenesis, and modulation of neuroinflammation. Although its expression declines in adulthood and becomes largely restricted to the hippocampus, brain injury or inflammatory insult upregulates GPR110. Activation of GPR110 by its endogenous ligand synaptamide has been shown to suppress pro-inflammatory cytokine production following lipopolysaccharide (LPS) exposure. However, the cell-type-specific role of GPR110 in regulating inflammation-associated behavioral changes remains unclear. Here, we tested whether conditional overexpression of GPR110 in CX3CR1+ microglia in adult mice modulates anxiety-like behavior following systemic LPS administration. LPS induced reduced locomotion and increased anxiety-like behavior in control mice, whereas these behavioral deficits were attenuated in mice overexpressing GPR110 in microglia. Notably, GPR110 knockout mice exhibit impaired learning and memory compared to wildtype controls. Conversely, mice with GPR110 overexpression in glutamatergic neurons produce the opposite effect, exhibiting improvements in learning and memory compared to wildtype controls. These findings support a broader role for GPR110 in cognitive function. Ongoing studies will determine whether microglial GPR110 overexpression produces similar effects on cognitive performance relative to GPR110 overexpression in glutamatergic neurons. Proteomic and immunohistochemical analyses are underway to define the molecular pathways underlying these effects. Together,

these findings implicate microglial GPR110 signaling as a regulator of neuroimmune-driven behavioral and cognitive outcomes.

Disclosures: M. Melkumyan: None. **B.X. Huang:** None. **H. Kim:** None. **D.M. Lovinger:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.02/FF20

Topic: G.03. Stress and the Brain

Support: R01MH133846

Title: RhoA Network Signaling Associates with Cognitive Performance and is Elevated by Chronic Stress

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Abstract: Chronic stress induces marked cognitive impairment and dendritic spine destabilization in hippocampal CA3 pyramidal neurons. A prior published genome-wide association meta-analysis identified RHOA as a hub gene influencing human cognition, implicating RhoA signaling in cognitive function. Whether altered RhoA network signaling is important for the effects of risk factors associated with increased susceptibility to cognitive impairment is largely unknown. To this end, we examined the effects of chronic stress, a well-established precipitating factor for the onset of psychiatric disorders typified by cognitive aberrations, on the RhoA signaling network in CA3. Young adult mice were exposed to an 8-day escalating intermittent restraint stress paradigm (control, n = 15; stress, n = 16). CA3 tissue was microdissected, homogenized, and subjected to subcellular fractionation and western blot analysis to characterize the expression profile and subcellular distribution of key RhoA signaling proteins across crude nuclear, cytosolic, and crude synaptosomal fractions. Exposure to chronic stress selectively increased synaptosomal PDZ-RhoGEF and RhoA expression by ~88% and ~74%, respectively (Holm-Šídák, p = 0.01, 0.04). No other examined components of the RhoA signaling network were altered. In a separate cohort of naïve wild-type mice (n = 19), below-average Y-maze performers exhibited elevated endogenous synaptosomal PDZ-RhoGEF expression (~40% increase; t-test, p = 0.03). Together, these findings identify PDZ-RhoGEF as a stress-responsive component of the RhoA signaling network and suggest that endogenous PDZ-RhoGEF levels are associated with individual differences in cognitive performance.

Disclosures: M. Avlas: None. **K.J. Bjornson:** None. **T.L. Ziehm:** None. **M.E. Cahill:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.03/FF21

Topic: G.03. Stress and the Brain

Support: National Institute of Environmental Health Sciences R00ES033256-03
National Institute of Environmental Health Sciences K99ES033256-02
The Pennsylvania State University Biobehavioral Health Department seed grant 150000009581

Title: Sex Differences in Cognitive and Affective Outcomes Following Perinatal Exposure to Organophosphate Flame-Retardants and Chronic Variable Mild Stress

Authors: *S. NEWMAN[1], A. DEFINA[2], J. J. CONNAGHAN, IV[5], I. N. BERNAL[6], Z. ARGOT[3], C. YANG[4], K. WIERSIELIS[1];
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Abstract: Endocrine disrupting compounds (EDCs) are chemicals that alter typical endocrine function. Flame-retardants are a subgroup of EDCs that are added to consumer products to reduce flammability and slow the ignition of fire. We have previously identified that perinatal exposure to organophosphate flame-retardants (OPFRs) and stress are known to disrupt cognition and anxiety-like behavior in a sex-dependent manner independently. Co-exposure to perinatal OPFRs and chronic stress on cognition and anxiety-like behavior is currently underexplored. Wild type dams were orally exposed to either oil or a mixture of OPFRs (tris(1,3-dichloro-2-propyl) phosphate, triphenyl phosphate, and tricresyl phosphate) from gestational day 7 to postnatal day 14. At 7-8 weeks, offspring were either unstressed or underwent chronic variable mild stress for 6 weeks. 13-14-week-old offspring underwent, the Y-maze, Open Field Test (OFT), Spatial Object Recognition (SOR), Novel Object Recognition (NOR), and short-term (ST) and long-term (LT) Barnes maze. In the Y-maze, stressed mice had greater unknown arm entries in contrast to unstressed mice, implying an increase in hippocampal-dependent spatial navigation memory. In the OFT, OPFR stressed females spent less time in the center compared to OPFR unstressed females, suggesting an anxiogenic phenotype. In the SOR, stressed mice interacted with the displaced object more than unstressed mice, indicating an increase in hippocampal-dependent memory for object configurations. In the NOR, oil stressed females spent more time with the novel object in contrast to oil unstressed females, suggesting an improvement hippocampal-independent memory. On the ST Barnes maze, OPFR stressed females had less head entries in the escape hole compared to OPFR unstressed females, indicating an impairment in this type of memory. OPFR unstressed females spent more head time in the escape hole in contrast to oil females in both stress conditions. On the LT Barnes maze, there were no differences in spatial navigation memory consolidation. Collectively, perinatal exposure to OPFRs and chronic stress alter cognition and anxiety-like behavior in a

sex-dependent manner. Future studies will investigate the underlying neural mechanisms through analyses of dendritic spine density, cFOS expression, and neurotransmitter content in brain regions involved in stress regulation and cognition.

Disclosures: S. Newman: None. **A. Defina:** None. **J.J. Connaghan:** None. **I.N. Bernal:** None. **Z. Argot:** None. **C. Yang:** None. **K. Wiersielis:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.04/FF22

Topic: G.03. Stress and the Brain

Support: NSERC Discovery Grant RGPIN-2019-04108

Title: Does short-term application of the stress hormone corticosterone to acutely prepared rat hippocampal slices affect surface expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)?

Authors: C. T. PHAN, *J. G. MIELKE;
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Abstract: Many studies have shown that brief application of the stress hormone corticosterone (CORT) increases glutamatergic neurotransmission in the hippocampus. To examine whether this increase in glutamatergic activity is related to changes in AMPAR expression at the cell membrane, dorsal hippocampal slices were prepared from 8-week-old male Sprague-Dawley rats and treated with either 200 nM CORT, or vehicle (0.01% dimethyl sulfoxide) for 30 minutes. In one set of experiments (n = 4), surface proteins were biotinylated immediately after treatment and then enriched using neutravidin conjugated beads following tissue homogenization. Next, surface and total AMPAR levels were estimated by measuring relative expression of the GluA1 and GluA2 subunits with Western blotting. CORT was found to cause a 37% decrease (SEM ± 2%, p = .0003, d = 9.5) in surface GluA1 expression and a 24% decrease in surface GluA2 expression (SEM ± 6%, p = .03, d = 1.8). These data suggest that CORT either causes an increase in the internalization, or a decrease in the insertion of AMPARs, particularly of GluA1-containing and GluA2-containing variants. In a different set of experiments (n = 6), AMPAR trafficking was assessed by examining GluA2 interaction with PICK1 and PSD-95 using co-immunoprecipitation. In particular, an increase in GluA2-PICK1 was taken to indicate greater AMPAR internalization and an increase in GluA2-PSD-95 was taken to indicate an increase in localization of AMPARs at the post-synaptic density. Notably, CORT treatment did not change GluA2 interaction with either PICK1, or PSD-95. A decrease in surface AMPAR expression without an accompanying change in GluA2 interaction with PICK1 suggests that CORT decreases the insertion of AMPAR into the cell membrane. Moreover, the absence of change in GluA2 interaction with PSD-95 suggests that the majority of the receptors affected by CORT

reside outside of the post-synaptic density, which agrees with the current theoretical model of AMPAR trafficking proposing the extra-synaptic membrane as the point of entry and exit of AMPARs to and from the cell membrane. Together, these data suggest that CORT may have an inhibitory effect on glutamatergic activity in adult hippocampal slices. Indeed, reducing the expression of AMPARs at the cell membrane may reflect a homeostatic response to the increase in glutamatergic activity caused by CORT. Given that our observations contradict the effect of CORT seen by other researchers in cultured hippocampal neurons and acute hippocampal slices, further work will be needed to confirm our findings and to determine whether they may be compatible with the results seen by others.

Disclosures: C.T. Phan: None. **J.G. Mielke:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.05/FF23

Topic: G.03. Stress and the Brain

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MH096889
MH126027
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DA050558-03
NSF GRFP DGE1845298
Canadian Institutes of Health Research: Project Grant 169203
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The Bren Foundation

Title: The role of high hippocampal estrogen levels, age, and sex-specific receptor signaling in memory problems induced by acute stress

Authors: *R. E. HOKENSON[1], K. RODRIGUEZ[2], Y. CHEN[1], B. DOCOLAS[3], J. WINTER[2], S. E. BRONECHTER[1], I. RAYNA[1], C. M. GALL[1], K. K. SOMA[3], E. A. HELLER[2], T. BARAM[1];
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Abstract: Background: It is now recognized that acute severe stresses (e.g., mass shootings, earthquakes) can provoke enduring disturbances of hippocampus-dependent memory, and that these problems are more common in women. Why do these sex differences exist? What are the implications for aging? Stress vastly elevates risk for Alzheimer's disease (AD) and related dementias, which are more common in women. While many studies focus on low estrogen levels during menopause, the potential role of high estrogen levels during the menopausal transition

(the perimenopause) in the onset of memory problems and AD has not been examined. These studies probe the roles of sex, age, and hormones on memory disruptions following acute stress. Methods: To probe the sex differences underlying memory vulnerability to stress, we modeled multiple acute concurrent stresses (MACS) in mice by imposing simultaneous physical, social, and emotional stresses for two hours. Studies were conducted in male, proestrus female (high estrogen), and estrus female (low estrogen) mice. We probed estrogen receptor (ER) contribution by treating mice with selective ER blockers or employing transgenic mice with selective, conditional deletion of ERα or ERβ (ERKO). Impacts on memory were assessed through several memory tests. To identify the mechanisms by which MACS enduringly disrupt memory, we tested differential gene expression and enrichment of permissive or repressive histone modifications in wild-type (WT) and ERKO hippocampus. To study the impact of high, "perimenopausal" estrogen levels and MACS on memory problems and AD pathology, middle aged (10 months) WT or AD (hAβ-KI$^{SWE/IBE}$ / hMAPT-H2) female mice were given subcutaneous estradiol pellets or placebo. Results: MACS enduringly disrupted memory in males and proestrus females, mice with high levels of hippocampal estrogen, while females stressed during estrus were protected. Pharmacological and transgenic approaches indicated signaling in ERα in males and, in contrast, ERβ in females, as mechanisms for these memory problems. MACS-vulnerable male and proestrus females had a higher prevalence of hippocampal permissive chromatin compared to estrus females. This heightened plasticity may be beneficial to memory at baseline but potentially maladaptive in the context of stress. Ongoing experiments investigate ER contribution to stress-vulnerability by probing differential gene expression and histone modifications in ERKO hippocampus. In aging female mice, elevating estrogen levels increased vulnerability to MACS-induced memory problems. Studies examining the impact of high estrogen levels during middle age on AD pathology are underway.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.06/FF24

Topic: G.03. Stress and the Brain

Support: Secihti CF-2023-G-243
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ZIAMH002386

Title: PACAP neurons of the bed nucleus of the anterior commissure coordinate basolateral amygdalar and anterior dorsal thalamic circuits during looming threat and memory-guided escape in a labyrinth

Authors: *L. ZHANG[1], V. S. HERNANDEZ[2], L. E. EIDEN[3];
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Abstract: Pituitary adenylate cyclase-activating polypeptide (PACAP) acts as a neurotransmitter in brain circuits recruited by stress and contributes to behavioral and endocrine adaptations to threat. However, the contribution of discrete forebrain PACAPergic nuclei to defensive behavior remains poorly understood. We investigated PACAP-expressing neurons of the bed nucleus of the anterior commissure (BAC), a small PACAP-rich glutamatergic nucleus located at the intersection of the anterior commissure, stria terminalis, stria medullaris, and fornix.Using PACAP-Cre mice and Cre-dependent viral tracing, we identified prominent BAC projections through major forebrain fiber systems to regions implicated in threat processing, emotional learning, and spatial orientation, including the lateral amygdala (LA), basolateral amygdala (BLA), posterior amygdala, hypothalamic nuclei, lateral habenula, and anterior dorsal thalamic nucleus (AD). These findings indicate that the BAC is not primarily commissural, as suggested by its name, but instead functions as a limbic integrative node embedded within major forebrain conduits.To examine BAC function, we developed a looming-threat learning and memory paradigm in which mice first learned the location of a shelter within a complex maze before exposure to an overhead looming stimulus. Chemogenetic inhibition of BAC PACAP neurons impaired shelter-directed escape, increased freezing, prolonged escape trajectories, and disrupted efficient safety-seeking behavior. Selective deletion of PACAP from BAC neurons reproduced these deficits, demonstrating a specific requirement for PACAP signaling within this circuit.Fos mapping revealed reduced activation of the posterior basolateral amygdala, ventral CA1, and anterior dorsal thalamic nucleus following BAC/PACAP manipulation. Because the AD contains head-direction neurons and participates in spatial orientation and memory circuits, these findings suggest that BAC PACAP neurons coordinate amygdalar threat processing with thalamo-hippocampal networks that guide navigation to safety.Together, these results identify the BAC as a previously unrecognized PACAPergic hub linking sensory threat processing, emotional learning, and spatially directed defensive behavior.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.07/FF25

Topic: G.03. Stress and the Brain

Support: R21MH114182
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PSC-CUNY Awards
The CUNY Graduate Center Dissertation Fellowship

Title: The Amygdala-Accumbens Pathway Contributes to Stress-Induced Social Avoidance

Authors: *J. LEE[1], S. HANIF[2], T. NABATIAN[3], G. LIFSHITS[4], E. LIKHTIK[4], N. S. BURGHARDT[5];
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Abstract: Chronic social defeat stress (CSDS) is a resident-intruder paradigm that reliably leads to social avoidance behavior. Studies investigating the neural basis of this response implicate the nucleus accumbens (NAc), which receives glutamatergic input from the basolateral amygdala (BLA). We began investigating whether BLA input to the NAc contributes to CSDS-induced social avoidance using immunocytochemistry. To visualize BLA-to-NAc projections, we injected a retrograde tracer (pAAVrg-hSyn-EYFP) bilaterally into the NAc of 129Sv/Ev male mice before exposing them to 10 days of CSDS (n=21) or control conditions (n=22). Mice were then perfused after being tested in the social interaction test with either a CD-1 mouse or a conspecific as the social target. Brains were stained for the neural activity marker c-Fos and co-labeled cells (EYFP+/c-Fos+) were quantified in the BLA. Consistent with our previous findings, defeated mice only avoided the CD-1, the strain used to induce CSDS, and not a conspecific. When the CD-1 was the social target, defeated mice had more co-labeled cells than non-defeated mice specifically in the posterior BLA ($p<0.01$), indicating more activity of these BLA-to-NAc projectors. This was not found when a conspecific was the social target. To test whether BLA input to the NAc is necessary for avoidance of the CD-1, we inhibited this pathway with chemogenetics during social interaction testing. Mice were injected bilaterally with a retrograde inhibitory DREADD (n=4) or control virus (n=12) into the NAc and implanted bilaterally with cannula above the BLA. All mice were defeated and then given a local infusion of clozapine-N-oxide (CNO) into the BLA immediately before social interaction testing (social target: CD-1). Surprisingly, inhibition did not affect social interaction on the day it was infused, but it prevented avoidance of the CD-1 when mice were tested drug-free the next day (Interaction time: DREADD virus = 177.8 sec; Control virus= 25.4 sec). This suggests that BLA input to the NAc is not necessary for the expression of social fear memory, but may be critically involved in memory reconsolidation. Lastly, we defeated mice and recorded local field potentials in the BLA and NAc during the social interaction test. We found that BLA theta power (3-7Hz) increased during avoidance of the CD-1 (n=6), but not when a conspecific was the social target (n=7). In ongoing analyses, we are characterizing BLA-NAc synchrony and the directionality of BLA-NAc communication. Together, these findings demonstrate that the BLA-to-NAc pathway plays a key role in CSDS-induced social avoidance, providing new insights into how fear and reward circuits interact.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.08/FF26

Topic: G.03. Stress and the Brain

Title: Age and Sex Dependent Effects of Acute Social Isolation in Rats Across Anxiety Endophenotypes: Prefrontal-Thalamic Circuit Mechanisms

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Abstract: Social interaction is a key component of neurodevelopment, and social isolation is a potent environmental stressor and significant risk factor for adverse long-term mental, physical, and cognitive health outcomes. Trait-like differences in anxiety represent a stable source of individual variability that may shape vulnerability to adverse social experiences. In the current study, we examined whether trait anxiety, age, and sex interact to influence behavioral and neural responses to acute social isolation (ASI) in rats. Adult and aged (n=32) male and female Long-Evans rats who were screened on the elevated plus maze (EPM) to assess endogenous variations in trait anxiety underwent baseline behavioral assays including the novel object recognition (NOR), open field (OF) test, and ultrasonic vocalization (USV) recordings. Rats were singly housed for 4 weeks (ASI) before being retested on the paradigms above. Following behavioral testing, rats were exposed to OF or remained in their homecage prior to being perfused. Brain tissue was processed for c-Fos immunohistochemistry to examine activity-dependent changes within prefrontal-thalamic-hippocampal-amygdala networks. Our results indicated that adult rats exhibited greater sensitivity to ASI than aged rats, as evidenced by increased novel object exploration. A two-way (age × condition) ANOVA revealed significant effects of age, $F(1, 26) = 5.223$, $p < .05$, and condition, $F(1, 26) = 4.666$, $p < 0.05$, in the OF, indicating that both age and ASI influenced exploratory behavior. We examined several USV acoustic parameters and found rats emitted more vocalizations following ASI, regardless of age, $F (1, 24) = 3.906$, $p= 0.06$, with a sex X condition interaction, $F (1, 17) = 9.648$, $p < 0.01$, such that aged female rats exhibited greater vocalizations. Lastly, open arm exploration in the EPM was significantly correlated with exploration of the center zone in the OF, regardless of age or condition, showing stability of anxiety endophenotypes. Increased avoidance was positively significantly correlated with frequency of USVs following ASI, demonstrating a relationship between anxiety endophenotypes and USV responses to social isolation. These findings indicate that age, sex, and anxiety-related avoidance traits are important determinants of susceptibility to ASI, providing insight into the mechanisms through which social experiences influence cognition and emotion.

Disclosures: A.G. Soto-Confer: None. **A. Martinson Reasoner:** None. **M. Awan:** None. **S.B. Linley:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.09/FF27

Topic: G.03. Stress and the Brain

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Developmental Neuroscience and Neurogenetics Program at The Saban Research Institute
Child and Brain Development Program of the Canadian Institute for Advanced Research
Animal Care Facility at The Saban Research Institute
USC Neuroscience Graduate Program

Title: Examining the influence of glucocorticoid receptor signaling in extinction engrams

Authors: *H. ADNEY[1,2,3], B. G. DIAS[4,1,2,3];
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Abstract: Post-traumatic stress disorder (PTSD) is a highly prevalent condition characterized by deficits in extinction recall, or the inability to recall learning that a cue previously associated with an aversive outcome is no longer dangerous. Efforts to remedy deficits in extinction recall have sought to determine the role of glucocorticoid receptors (GRs) in extinction learning and recall given the highly conserved physiological release of glucocorticoids that bind to GRs upon encountering threatening cues. While informative, the typically used approaches of systemic and pharmacological antagonism of GRs do not allow selective targeting of GRs within ensembles of neurons that are active during extinction learning and recall - extinction engrams. We investigated the relevance of GRs in extinction learning ensembles for extinction recall by utilizing an auditory fear conditioning protocol in mice. Specifically, we selectively knocked out GR-exon2 in extinction learning ensembles in adult mice by crossing mice with Fos-TRAP, floxed-tdtomato, and floxed-GR-exon2- transgenes while administering i.p. tamoxifen injections at extinction learning. This strategy resulted in mice that either had GR-exon2-knocked out (GRKO) or intact (GR Intact) in ensembles of cells that were active during extinction training (n = 12-16 mice/group/sex). All mice recalled conditioned fear (males: $p = 0.53$, females: $p = 0.68$) and acquired extinction learning to the same degree (males: $p = 0.38$, females: $p = 0.95$). Five days following the knockout of GR-exon2 in extinction learning ensembles, recall of extinction learning was assessed. In both males and females, there was no significant difference between GRKO and GR Intact groups (males: $p = 0.06$, females: $p = 0.22$). These results suggest that the impairment of GR genomic signaling - via knockout of its transactivation domain - in extinction learning ensembles does not interfere with the recall of extinction learning.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.10/FF28

Topic: G.03. Stress and the Brain

Support: ZIC-ES103330

Title: Low frequency Type II theta dynamics in the dorsal hippocampus reflect threat processing in mice

Authors: *K. D. STEVANOVIC[1], E. E. THOMSON[2], J. D. CUSHMAN[1];
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Abstract: Type II theta oscillations (4-7 Hz) in the hippocampus are typically observed during immobility, are sensitive to cholinergic antagonism and have been implicated in anxiety and fear. Its precise contribution and underlying mechanisms are understudied and poorly understood. The objective of this study was to elucidate the role of Type II theta oscillations in dorsal hippocampus-dependent fear learning, with a focus on threat processing. We conducted wireless local field potential (LFP) recordings from the stratum lacunosum-moleculare of dorsal CA1 in wild-type C57BL/6J mice during a trace fear conditioning paradigm, which requires hippocampal processing. Mice received five tone (20 s, 75 dB 2800 Hz)-shock (2s, .5 mA) pairings with a 20s trace interval separating the tone and shock. Freezing behavior, a measure of learned fear and threat assessment, was quantified throughout acquisition, context, and tone tests. In addition, we assessed open field exploratory behavior in novel and familiar environments. LFP spectrograms were analyzed to extract peak theta frequencies, and kernel density estimation was used to objectively distinguish low (Type II, 4-7 Hz) and high (Type I, 7-10 Hz) theta modes. A theta ratio, reflecting the relative dominance of low vs. high theta, was computed moment-by-moment for each animal and correlated with behavioral (freezing, motion, acceleration) and task epoch parameters. We developed Neurodash, a browser-based graphical user interface to facilitate initial analysis of behavioral and neural signals. Results showed that, during successful acquisition and retrieval of fear memory, there was a significant increase in Type II theta power, especially during freezing behavior, consistent with a role for this oscillation in threat processing. In contrast, high-frequency theta was more prominent during active movement, as expected. The theta ratio robustly tracked behavioral state transitions, with sharp increases in low theta corresponding to periods of freezing and threat anticipation. Detailed analysis and comparison with open field exploratory behavior argues that the Type II theta represents a distinct oscillatory state and not simply the loss of Type I due to immobility. We propose that Type II theta reflects a distinct state of active attentional sampling that is distinguishable from mobility-related Type I theta and inattentive immobility. This work highlights the unique role of Type II theta in orchestrating hippocampal network dynamics during threat processing and provides new analytic tools for dissecting theta substructure in real time during complex behaviors.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR278.11/FF29

Topic: G.03. Stress and the Brain

Support: R01DA049837
R01DA056534
R21DA062844

Title: Early resource scarcity alters visuospatial associative memory in adult rats

Authors: *D. K. SHROFF[1,2], N. EDWARDS[2,1], J. NYAKOA[2,1], K. MESAPE[2,1], E. P. HARRIS[2,1], D. A. BANGASSER[2,1];
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Abstract: Early resource scarcity contributes to cognitive changes and neuropsychiatric disorders later in life, yet the underlying neural mechanisms remain poorly understood. To model early resource scarcity, we use the limited bedding and nesting (LBN) manipulation in rats. In LBN, during postnatal days 2-9, rat dams and pups are placed in an impoverished cage environment lined with a metal grate to prevent access to bedding, only a paper towel for nesting material, and no enrichment tube is provided. Control rats are reared in a standard cage environment with ample access to bedding, nesting material, and an enrichment tube. LBN alters the development of brain regions involved in higher-order cognition, including the hippocampus and the prefrontal cortex. To further understand how these neurodevelopmental changes influence cognition in adulthood, we assess male and female rats using the Barnes maze and touchscreen-based Paired-Associates Learning task. The Barnes Maze is a low-stress alternative to the Morris Water Maze (MWM), which assesses spatial learning, memory, and cognitive flexibility. The PAL task is based on the human Cambridge Neuropsychological Test Automated Battery. It is designed to evaluate deficits in visuospatial associative memory by training rats to distinguish object-location associations using touchscreen operant chambers. Previous literature has found that LBN impairs spatial memory in males in the MWM (females not tested) but increases associative fear learning in females. We found that LBN does not disrupt spatial memory on the Barnes maze in both sexes but enhances visuospatial associative learning on PAL only in LBN females. Collectively, these studies aim to advance our understanding of sex-biased effects of early resource scarcity on cognition. This will lay the groundwork for understanding the mechanistic basis for how developmental stress promotes risk and resilience to later cognitive changes and ultimately lead to targeted interventions to promote brain health.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR278.12/FF30

Topic: G.03. Stress and the Brain

Support: DoD W81XWH-20-1-0066

Title: Gonadal hormones on the day of trauma modulates PTSD development and future risk for cardiovascular abnormalities in females

Authors: *C. V. CHEN;
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Abstract: Post-traumatic stress disorder (PTSD) is a deleterious mental health condition with a lifetime prevalence of 6-9% in the US, affecting twice as many women as men. In addition, women with PTSD exhibit higher risk and incidence of cardiovascular disease. Using a PTSD rodent model, Single Prolonged Stress (SPS), we sought to determine how estrous cycle stage on the day of trauma affect development of PTSD-like symptomatology and, whether this, in turn, affects future heart function. We demonstrate that experiencing trauma on the day of proestrus increases the risk of developing extinction recall deficits, a cardinal deficit in PTSD patients. In addition, both trauma and PTSD symptomology development is associated with later abnormal heart function.

Disclosures: C.V. Chen: None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.13/FF31

Topic: G.03. Stress and the Brain

Title: Impact of forced confabulation on the generation of false memories for a laboratory-controlled stress experience

Authors: *H. G. SPITLER, K. M. REEVES, R. A. MORRIS, B. R. COMER, J. L. KIRKLAND, N. E. PORTER, S. M. WOOD, J. N. GROSS, M. E. PAPHANCHITH, K. R. MCCLENEN, K. E. PAYMENT, P. R. ZOLADZ;
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Abstract: Because stress enhances memory for the central details of an experience, it is possible that stress may also reduce the likelihood of forming false memories about that experience. Here, we examined the impact of a forced confabulation manipulation on the development of false memories for a stressful event. On Day 1, participants were exposed to the Trier Social Stress Test (TSST; stress condition) or to the friendly-TSST (f-TSST; non-stress condition), both of which were designed to enable participant memory of the experiences to be quantified. The TSST required participants to deliver a speech in front of two lab panel members; the f-TSST required participants to casually converse with panel members about their interests. In both conditions, the panel members interacted with (central objects) or did not interact with (peripheral objects) several objects sitting on a desk in front of them. The next day, participants returned to the lab to answer several questions about the experience from Day 1 (including the objects that were present); some questions forced participants to confabulate answers. Three days later, participants were given a test that asked them to determine which events occurred during the experience on Day 1 and which did not; participants also provided confidence ratings for their answers. After this test, participants were asked to recall as many objects from the Day 1 experience as they could. There was a statistical trend suggesting that, relative to non-stressed participants, stressed participants tended to exhibit less false memory for central objects and greater false memory for peripheral objects. This trend was supported by a significant effect of stress on participants' confidence ratings. Relative to non-stressed participants, stressed participants were more confident that false events involving central objects did not occur; the opposite was true for events involving peripheral objects. Consistent with past work, stressed participants exhibited greater object recall than non-stressed participants, an effect driven by enhanced central object memory in stressed participants. These findings suggest that stress may not only enhance memory for central details of an event; it may also reduce that memory's susceptibility to false information.

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Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.14/FF32

Topic: G.03. Stress and the Brain

Support: NIH grant R01AA031072

Title: Trauma history shapes neural and subjective metrics of responses to and memory for stress

Authors: *Y. FARTACHUK, T. HAN, J. YE, J. G. PRATT, F. A. HARDI, E. V. GOLDFARB; Yale Univ., New Haven, CT

Abstract: Past trauma can alter future stress responses. Our recent work has shown that neural representations of past trauma are engaged in real time after stress, but the consequences of these acute stress responses for adaptive coping and later memory are unclear. Here we ask how trauma exposure influences neural and subjective responses to stressors in the laboratory, and the way that real-world stressful experiences are remembered.
Healthy adults (N=34, data collection ongoing) completed an fMRI protocol comprising an in-scan multisensory stress condition and matched control condition on separate days, rating their subjective stress and focus. Lifetime trauma exposure was indexed by the Life Events Checklist. Participants then completed a three-week smartphone protocol with daily encoding surveys and next-day retrieval surveys assessing memory accuracy for personal stressful events. Trauma brain network was previously identified using an independent sample (Hardi et al, 2025) using functional connectivity (FC) neuroimaging data. Linear mixed effects models confirmed that the in-scan stress condition successfully increased subjective stress levels across participants ($b=2.59$, $p<.001$). Trauma brain network was attenuated in relation to subjective stress during stress condition (vs. control; condition x FC: $b=-16.34$, $p=.018$). Moreover, individuals exposed to more lifetime trauma reported greater focus during stress, but not control (condition x trauma interaction: $b=0.07$, $p<.001$), and this increased focus during stress in the lab was related to more accurate memory features for out-of-lab stress events ($b=0.005$, $p=.023$). These preliminary findings inform models of trauma effects on stress reactivity and adaptive stress responses through neural and memory pathways. Consistent with the habituation model, trauma brain network was attenuated during stress, potentially reflecting an adaptive response to acute stress. This adaptation may operate through cognitive mechanisms sustained by increased focus during stress, which support memory accuracy during stressful moments in the real world.

Disclosures: Y. Fartachuk: None. **T. Han:** None. **J. Ye:** None. **J.G. Pratt:** None. **F.A. Hardi:** None. **E.V. Goldfarb:** None.

Poster

PSTR278: Stress-Modulated Pathways: Cognition, Learning, and Memory Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR278.15/GG1

Topic: G.03. Stress and the Brain

Support: NSF Award #2137255

Title: Understanding the Neural Mechanisms of Emotional Well-Being During Nature Exposure Through Mobile Brain-Body Imaging

Authors: *D. G. HERNANDEZ SOLIS[1,5], Y. E. LIMA CARMONA[2], B. RAMÍREZ ZAMORA[5], N. SANTIAGO ANTONIO[6], A. QUINTERO LEAL[5], D. DAS[3], J. L. CONTRERAS-VIDAL[4];
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Houston, Houston, TX; [5]Sch. of Engin. and Sci., Tecnológico de Monterrey, Monterrey, Mexico; [6]Sch. of Engin. and Sci., Tecnológico de Monterrey, General Zuazua, Mexico

Abstract: Mental health disorders represent a growing health challenge due to the development of urbanized environments. Nature exposure has been associated with improvements in Emotional Well-Being (EWB), stress reduction, and attentional restoration. However, the neural mechanisms underlying the impact on nature on the brain remain understudied. In this study, we investigate the impact of nature exposure using Mobile Brain-Body Imaging (MoBI). Electroencephalographic (EEG) data of 20 healthy participants (10 males; age 23.6 ± 2.8) was recorded with an 8-channel LiveAmp system while being exposed to real-world nature stimuli in the Japanese Garden at Hermann Park (Houston, Texas). Additionally, synchronized data from weather, audiovisual recordings, and geolocation were collected throughout each session, with psychological assessments (POMS/STAI) before and after nature exposure. A multimodal pipeline, including band-pass filtering [0.1-50 Hz], H-infinity filters for eye and motion artifacts removal, Artifact Subspace Reconstruction, Common Average Re-referencing, Independent Component Analysis was used for EEG denoising; moreover, dipole fitting was used to identify sources of brain activity. Preliminary clustering analysis of cortical sources demonstrated consistent spatial patterns across participants, with five of the six participants exhibiting localized activity of regions associated with motor planning (BA 6), somatosensory integration (BA 5), visuospatial processing (BA 7), attentional control (BA 9), executive function (BA 46), and visual perception (BA 17/18/19). The occipital clusters showcase consistent activity related to visual stimuli, engaging the participant during nature viewing. The frontal and sensorimotor clusters represent the execution of attentional and sensorimotor systems. Spectral analysis on all identified clusters revealed predominance of alpha (α) activity relative to beta-band activity. The sources with strongest α activity were found in the temporal region of the brain (BA 20/21/22/37), while the parieto-occipital regions (BA 7/19) present elevated α activity. Psychological assessments demonstrated significant reductions in anxiety following nature exposure (STAI $p<0.001$), while POMS scores presented a decrease in tension, anger, fatigue, confusion, and total mood disturbance (all, $p<0.05$). We hypothesize that brain synchrony, particularly within α networks, across these brain regions, may contribute to the psychological improvements by the presence of natural stimulus, providing a shared temporal structure supporting attention and EWB.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.01/GG2

Topic: G.07. Biological Rhythms and Sleep

Support: NIMH F32NS142584
Howard Hughes Medical Institute

Title: Somnus: a tunable, open-source platform for automated EEG scoring in physiological and disease mouse models

Authors: *J. M. BRENNER[1], M. S. CAUDILL[2], H. Y. ZOGHBI[3];
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Abstract: While sleep state can be inferred from EEG and EMG activity, leading automated detection models are often prohibitively expensive or lack the flexibility needed for diverse experimental conditions. Bandwidths, sleep patterns, and artifacts can vary significantly between animal backgrounds and specific disease models, leading to inaccurate scoring when using rigid, black-box algorithms. To address this, we developed Somnus: a tunable open-source automated sleep scorer designed to detect mouse sleep states across a range of physiological and pathological models. Somnus utilizes EMG power alongside delta and theta EEG band power in a logistic model that accurately categorizes wakeful, NREM, and REM states. Somnus is written in Python and features an accessible GUI with a fine-tuning suite to retrain the model on custom datasets. To aid in fine-tuning, Somnus automatically flags epochs with high algorithmic uncertainty for targeted manual review and subsequent retraining. This ensures accurate results across a range of mouse models without requiring laborious manual scoring of entire datasets. Somnus thus provides a freely accessible, adaptable, and highly accurate alternative to commercial sleep-scoring software.

Disclosures: J.M. Brenner: None. **M.S. Caudill:** None. **H.Y. Zoghbi:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.02/GG3

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R35NS132160
NIH Grant R01NS117929

Title: Investigation of the Sleep-Relevant G Protein-Coupled Receptor Beta-1 Adrenergic Receptor

Authors: *H. KURANI;
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Abstract: Healthy sleep is essential for maintaining cognitive, metabolic, and physiological function. It is regulated by two major processes: the circadian rhythm, which governs sleep

timing, and sleep homeostasis, which governs sleep duration and quality. Many of these traits are under genetic control, and disruption of this balance can lead to sleep-related disorders. Despite its importance, the molecular mechanisms underlying sleep homeostasis remain poorly understood. Human genetics provides a powerful entry point: individuals with the familial natural short sleep (FNSS) trait sleep only 4-6.5 hours per night without adverse health consequences. Several missense mutations in G protein-coupled receptors (GPCRs) have been reported to cause the FNSS phenotype, including a mutation in beta-1 adrenergic receptor (ADRB1), in which alanine at position 187 is substituted with valine (A187V). To investigate the protein interaction landscape affected by this mutation, global proteomics, phosphoproteomics, and proximity labeling proteomics, mediated by engineered ascorbic peroxidase 2 (APEX2), will be employed. In this study, polyclonal and monoclonal HEK293T lines expressing the wild-type (WT) or mutant (A187V) forms of ADRB1, with and without a C-terminal APEX2 tag, were generated and characterized using flow cytometry, cAMP assays, immunofluorescence imaging, and Western blotting (WB). Results indicated that adding APEX2 to the V477 site on ADRB1 does not alter receptor dynamics across WT and A187V lines. These studies also identified the most suitable monoclonal cell lines expressing ADRB1-WT, ADRB1-A187V, and their APEX2 counterparts for downstream proteomics analysis; chosen lines showed preserved signaling and trafficking, proper plasma membrane localization of ADRB1, and confirmed ADRB1 protein expression levels and biotinylation efficiencies for APEX2 lines. Uncovering GPCR signaling networks regulating sleep homeostasis in FNSS may provide novel therapeutic targets to improve sleep quality and treat sleep disorders.

Disclosures: H. Kurani: None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.03/GG4

Topic: G.07. Biological Rhythms and Sleep

Title: Time of administration determines the effect of caffeine on sleep architecture: a telemetric EEG study in the healthy macaque

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Abstract: Caffeine is the most widely consumed psychostimulant, yet how the timing of intake relative to the rest/active cycle shapes sleep architecture remains poorly characterised in non-human primates. In this study, we examined the dose- and time-dependent effects of caffeine on vigilance states in the healthy macaque (Macaca mulatta) using chronic radiotelemetry.Six males were implanted intraperitoneally with three-channel biopotential telemetry transmitters that

recorded electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG) in unrestrained animals. Caffeine (1, 3, 6, and 30 mg/kg, per os) and vehicle were administered in a counterbalanced, repeated-measures design with a minimum 72 h washout. Two administration times were compared: lights-off (zeitgeber time, ZT12) and lights-on (ZT0). The 8 h post-ZT12 window was scored in 20 s epochs (Rechtschaffen and Kales criteria) as wake, light sleep (N1-N2), slow-wave sleep (N3) and rapid eye movement (REM) sleep by a rater blinded to treatment, using video verification. State durations, latencies, transitions and fast Fourier transform spectral power (delta-gamma) were quantified, with group comparisons by one-way ANOVA and Dunnett's post-hoc test.Recordings were obtained for all six animals in all conditions. Caffeine produced a dose-related increase in wakefulness, accompanied by reductions in slow-wave and REM sleep, with the effect being most pronounced at the highest dose. Notably, this sleep-disrupting action was more marked when caffeine was administered at lights-off, coinciding with the onset of the principal rest phase, than at lights-on. Detailed quantification of state durations, latencies and spectral power is ongoing.These data establish the macaque as a translational model for circadian-dependent psychostimulant effects on sleep and indicate that intake time is a key determinant of caffeine's impact on sleep architecture, with direct relevance to human consumption patterns.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.04/GG5

Topic: G.07. Biological Rhythms and Sleep

Title: Modafinil effects on sleep wake regulation in rats with or without sleep deprivation

Authors: *D. PUSHETT, G. PEYON, D. BABIN, M. MARTINEAU, E. ESNEAULT; Porsolt, Le Genest St Isle, France

Abstract: Modafinil is a wake-promoting agent clinically used to treat excessive daytime sleepiness associated with disorders such as narcolepsy, obstructive sleep apnea, and shift work sleep disorder. Owing to its well-characterized effects on wakefulness and sleep regulation, modafinil is commonly used as a reference compound in preclinical studies investigating sleep-wake mechanisms. The present study evaluated the effects of modafinil on sleep-wake architecture in rats under baseline conditions and following 6 h of sleep deprivation induced by the disk-over-water method. Rats were implanted with epidural EEG electrodes and stereotaxically placed hippocampal depth electrodes. EEG and locomotor activity were recorded continuously for 23 h using a telemetry system equipped with an accelerometer. Vigilance states

(wakefulness, rapid-eye movement (REM) sleep, and non-REM (NREM) sleep) were determined by spectral analysis of EEG signals. Sleep deprivation was induced using the disk-over-water method for 6 h, followed immediately by recovery recordings. In both experimental paradigms, modafinil (100 mg/kg, i.p.) was administered before the onset of the dark phase and EEG recording. Under baseline conditions, modafinil induced a pronounced increase in wakefulness during the first 4 h after administration, accompanied by marked reductions in both NREM and REM sleep. Following sleep deprivation, vehicle-treated animals exhibited the expected rebound increase in NREM and REM sleep during the recovery period. In contrast, modafinil significantly attenuated this rebound response, maintaining elevated wakefulness and suppressing both NREM and REM sleep during the first 4 h post-treatment. These findings confirm the robust wake-promoting effects of modafinil regardless of sleep pressure levels, effectively overriding homeostatic sleep drive. The results further support the utility of modafinil as a reference compound in preclinical studies of sleep-wake regulation and sleep homeostasis.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.05/GG6

Topic: G.07. Biological Rhythms and Sleep

Support: R01-HL155986

Title: Unbiased genetics identifies a glutamatergic signaling network as a mediator of daily sleep patterns

Authors: *A. L. RAVENS[1], S. GRIZZARD[2], J. S. LORD[4], S. SLEIMAN[3], K. K. JOYCE[1], K. DONOHUE[5], B. F. O'HARA[6], T. KAFRI[4], G. H. DIERING[7];
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Abstract: Sleep is a fundamental, evolutionarily conserved behavior essential for survival across animal species. Daily sleep patterns are regulated by a poorly understood interaction between the circadian rhythm (CR), which regulates sleep timing, and a homeostatic sleep drive that accumulates with time awake. While the CR is driven by molecular oscillations of “clock genes” in nearly all cells, the cellular mechanisms underlying sleep homeostasis remain largely unknown. Emerging evidence identifies neuronal synapses as a cellular locus of sleep need accumulation and resolution. Consistent with this model, previous efforts to identify molecular regulators of sleep need have implicated the activity-dependent synaptic gene Homer1a. To

advance mechanistic understanding of how synaptic function contributes to sleep regulation, we characterized daily sleep patterns in genetically diverse mouse strains from the Collaborative Cross. Strains exhibiting highly consolidated or fragmented sleep were selected for genetic analysis using quantitative trait loci (QTL) mapping. In F2 hybrids, 19 of 32 measures of sleep and circadian behavior mapped to a narrow QTL containing GRM5, which encodes a postsynaptic glutamate receptor and Homer1a binding partner, and GCPII, an astrocytic enzyme that regulates levels of N-acetylaspartylglutamate (NAAG), an agonist of the presynaptic and astrocytic glutamate receptor GRM3. Pharmacological manipulation of GRM5, GCPII, and GRM3 robustly altered sleep behavior, providing functional validation of these candidate genes. Together, these findings identify glutamatergic signaling across the tripartite synapse as a regulator of sleep behavior and support a model in which synapses act as a cellular site for the integration of circadian and homeostatic sleep signals.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: G.07. Biological Rhythms and Sleep

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Title: Potassium channels orchestrate the frequency and power of Slow Wave Activity in mice

Authors: *M. BALLESTER ROIG[1], K. ODE[2], R. YAMADA[1], E. ZHANG[2], S. SHI[3], K. KOMPOTIS[4], M. GJIKOLAJ[5], F. L. KINOSHITA[2], H. FUJISHIMA[1], M. D. BELLE[6], K. SUMIYAMA[7], H. R. UEDA[8];
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Abstract: Slow neuronal synchronies in the cerebral cortex - slow wave activity (SWA; <4 Hz) - are a signature of deep restorative sleep and a metric of sleep need. Recent research suggests that slower (<1 Hz) and faster (1-4 Hz) frequencies of SWA mediate distinct cognitive benefits, but the mechanisms governing this oscillatory speed remain unknown. We hypothesized that voltage-gated potassium channels (K_v) and hyperpolarization- and cyclic nucleotide-gated potassium/sodium channels (Hcn), which are critical for neuronal bursting, also shape sleep and the frequency of sleep brain oscillations. To test this, we combined three approaches: 1) recorded K_v or Hcn knockout (KO) mice using the respiration-based Snappy Sleep Stager (SSS) and/or electroencephalography (EEG); 2) performed adult, neuron-specific gain- and loss-of-function manipulations of Kv/Hcn channels using AAV-mediated gene delivery followed by EEG recording; and 3) examined how K_v/Hcn channels influence the hypnotic and SWA-inducing effects of sedative drugs. Across 42 Kv-channel knockout lines, we found that mice lacking the heart-related slowly-activating potassium channel subunits Kcnq1 and Kcne1 slept 2.5 to 3 hours less per day, and exhibited slower SWA frequency. In contrast, adult downregulation of Kcnq2 reduced SWA power without altering peak frequency, whereas boosting Kcnq2 currents specifically in excitatory neurons selectively increased SWA power. Consistent with a role for M-current in regulating sleep oscillations, knockout of seven PKC genes identified PKCγ as an additional regulator of SWA amplitude. Hcn channels exerted a distinct influence on sleep rhythms. Downregulating either Hcn1 or Hcn2 channels in excitatory neurons slowed the SWA frequency by ~1 Hz and increased SWA power by 10-30%. Notably, downregulating Hcn2 in excitatory cortical neurons also slowed down the frequency of NREM slow waves, implicating these channels in top-down cortical control of sleep rhythms. Mouse brain slice recordings of pyramidal neurons from cortical layer V suggest that Hcn channels regulate SWA by modulating neuronal excitability. Beyond their role in shaping basal sleep oscillations, Hcn channels (but not Kcnq channels) were required for normal homeostatic increases in SWA after sleep deprivation. In addition, dexmedetomidine, a sedative α2-adrenergic receptor agonist with acute antidepressant properties, required Hcn2 for its normal sleep- and SWA-inducing effects.These findings reveal that potassium channels in excitatory neurons play causal and dissociable roles in tuning SWA power and frequency, providing insights into the molecular mechanisms of sleep quality.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.07/GG8

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant 1R01NS147124-01

Title: Parafacial Zone Neuronal Activity in Relation to Cortical Slow-Waves

Authors: *M. ARAI[1], Z. ZHOU[2], H. S. GOMPF[3], C. ANACLET[3], N. P. PEDERSEN[4]; [2]Anesthesiol. and Pain Med., [3]Neurolog. Surgery, [4]Neurol., [1]Univ. of California Davis, Davis, CA

Abstract: The parafacial zone (PZ), located in the medulla just dorsal to the facial nerve, plays a key role in the induction and maintenance of slow-wave sleep (SWS). Previous work from our group showed that GABAergic PZ neurons sustain cortical slow-wave activity (SWA) and increase SWS duration at the expense of wake and REM sleep (Anaclet et al., 2014). Our overall objective is to define the neural circuits and dynamics underlying PZ-cortical interactions. As a first step, we are performing in vivo electrophysiology in lightly urethane-anesthetized mice, using dual silicon probe recordings from the PZ and forebrain regions, including the frontal cortex. Urethane was selected for its ability to induce two alternating sleep-like states: a deactivated state characterized by cortical slow waves and an activated state characterized by hippocampal theta activity. These experiments serve as a prelude to studies of spontaneous sleep-wake states and allow us to examine the emerging role of the PZ in the action of anesthetic drugs. A few recent studies suggest that the PZ may play a role in anesthetic induction and maintenance. Chemogenetic activation of PZ GABAergic neurons increases sensitivity to sevoflurane anesthesia (Luo et al., 2025). Similarly, hypnotic doses of isoflurane increase c-Fos expression in PZ GABAergic neurons, and ablation of these neurons produces behavioral resistance to isoflurane- and sevoflurane-induced hypnosis (Imamura et al., 2025). However, PZ firing patterns and their relationship to cortical activity during anesthesia remain unknown. Preliminary results show tonic firing (5-20 Hz) in the PZ during periods of high cortical SWA. During these periods, spike-triggered average analysis did not reveal clear frequency coupling between PZ unit activity and cortical activity. In contrast, during low-SWA periods characterized by burst suppression, PZ firing rates were lower (1-6Hz), and cortical SWA was aligned with PZ spike timing. These results suggest that tonic firing of PZ GABAergic neurons may contribute to high cortical SWA. Future studies will extend this work to freely behaving mice using Neuropixels probes to assess PZ-forebrain network dynamics across spontaneous sleep-wake states.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

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Whitehall Foundation

Title: Developmental emergence of sleep-dependent synaptic regulation

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Abstract: Early brain development is foundational for establishing neurotypical sensory, cognitive, and behavioral modalities. A growing body of experimental and theoretical work suggests the excitation/inhibition (E/I) ratio in both humans and animal models is integral to optimizing the circuits underlying these modalities. Previous work from our lab shows that the E/I ratio fluctuates across the 24h day in the primary visual cortex (V1) of adolescent mice, and is dependent on the sleep/wake cycle. However, it is unknown when sleep emerges in development as a regulator of the E/I ratio. Using whole-cell patch clamp, we measured miniature excitatory and inhibitory postsynaptic currents (mE/IPSCs) from V1 following either the sleep- or wake-rich phase in mice at different ages in early postnatal development. We found that sleep-dependent E/I regulation emerges at the beginning of the critical period (CP) for ocular dominance plasticity (ODP), when V1 becomes highly malleable to experience. We hypothesized that sleep-dependent regulation of E/I, whereby the E/I ratio decreases during the sleep-rich phase in V1, serves a functional role in CP opening. Maturation of inhibitory circuitry opens the CP, so to delay inhibitory maturation and thus CP opening, we used a mouse model expressing inhibitory DREADDs in inhibitory interneurons. We chronically delivered a DREADD agonist to either prevent the CP from opening at the typical juvenile age, or by delaying opening into adulthood, then performed two experiments: first, we confirmed CP timing in our DREADD model by performing monocular deprivation and then measuring the presence of interneuronal gamma rhythms (ING) in the contralateral binocular region of V1 as a proxy for CP plasticity; second, we recorded mE/IPSCs to observe E/I regulation in V1 following the wake- and sleep-rich phases. We found that sleep-dependent E/I regulation does not yet come online when CP opening is absent. However, when CP is opened in adulthood, sleep-dependent E/I regulation is present. Next, we tested whether sleep-dependent E/I regulation is a causal mechanism for ODP induction. We sleep-deprived mice before monocular deprivation, then measured ING. Strikingly, we found that sleep deprivation prevents ING rhythms, indicating that CP ODP is absent, as opposed to rested controls. These results show that the increase in inhibition that is known to promote brain maturation is required for E/I regulation to come online as a function of sleep early in development. Once online, sleep-dependent E/I reduction enables monocular deprivation to induce ODP.

Disclosures: B. Menarchek: None. **K. Schooling:** None. **M. Bridi:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

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Program #/Poster #: PSTR279.09/GG10

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Title: Mutations in antimicrobial peptides differently affect sleep and plasticity

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Abstract: Sleep and immunity are closely linked. Sleep loss is associated with decreased immunity, whereas immune activation increases sleep. Sleep loss also impacts learning and memory. In *Drosophila*, infection stimulates the systemic release of a battery of positively charged peptides called anti-microbial peptides (AMPs). These fly immune effectors have been understudied for their role in modulating sleep and sleep functions.We have been studying flies carrying mutations in various anti-microbial peptides (AMPs) to understand the link between sleep and immunity. We find that AMP mutants sleep less, and sleep lighter. Different AMP knockouts cause sex-specific sleep perturbations, with males and females exhibiting distinct patterns of daytime sleep, nighttime sleep, and sleep latency. Notably, the Group C mutant flies, a combined mutant for the anti-fungal peptides Metchinikowin (Mtk) and Drosomycin (Drs), exhibited the greatest impairments in sleep and an exaggerated sleep rebound upon sleep loss. The sleep rebound was unaltered in other AMP mutants. Different sets of AMP mutants exhibited specific disruptions in socialization and rocking-induced sleep, and sleep plasticity upon starvation. These data are a detailed characterization of sleep regulation in AMP mutants. We also evaluated sleep functions in these mutants. Group C mutants uniquely exhibited normal learning and memory, and lower synapse abundance, despite sleeping the least. Group C mutants are thus able to carry out some sleep functions despite their low sleep. Glial knockdown of Mtk and Drs mimicked the sleep phenotypes of the null mutants, indicating that these genes act via glia. Further, glial rescue of Drs rescued the sleep defects exhibited by the single Drs mutant. Finally, sleep and memory defects in AMP mutants were reversible - enhancing the sleep of short-sleeping Bomanin mutants pharmacologically or behaviourally improved learning and memory.Together, these findings suggest that AMPs are powerful modulators of sleep, and that different classes of AMPs influence sleep and sleep-dependent outcomes in distinct ways

through mechanisms that are still not fully understood. This also indicates that their effects are likely not simply due to a shared mechanism such as membrane disruption, which is a well-known property of these cationic peptides as immune effectors.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

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Topic: G.07. Biological Rhythms and Sleep

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Title: NREM sleep-inducing SIK3 signaling pathway regulates synaptic potentiation.

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Abstract: As wakefulness is prolonged, sleep pressure (i.e., sleepiness) increases and promotes sleep. However, the biological substrate of sleep pressure remains unclear. The synaptic homeostasis hypothesis proposes that synaptic potentiation accumulated during wakefulness is counterbalanced during sleep (Tononi & Cirelli, 2006). Previous studies have reported a correlation between sleep pressure and synaptic potentiation (De Vivo et al., 2017; Diering et al.,2017). We recently found that, in excitatory neurons of the prefrontal cortex (PFC), dendritic spine enlargement functions as sleep pressure and increases both the amount and depth of NREM sleep (Sawada et al., 2024). However, the molecular mechanisms underlying this process remain unknown. Here, we focused on the SIK3 signaling pathway in excitatory neurons, which has been implicated as a positive regulator of NREM sleep (Funato et al., 2016; Kim et al., 2022). Single-cell RNA-sequencing analysis of mice expressing the gain-of-function SIK3(Sleepy) mutant in excitatory neurons further suggests that SIK3 regulates the transcription of factors involved in synaptic plasticity (Kim et al., 2022).We therefore investigated whether SIK3 is involved in synaptic-potentiation-dependent induction of NREM sleep and increase in delta power, an electrophysiological marker of sleep pressure. Using SYNCit-K, a molecular tool that induces dendritic spine enlargement and promote sleep when activated in PFC excitatory neuron (Sawada et al., 2024), we found that SYNCit-K-dependent induction of NREM sleep was abolished in mice lacking SIK3 broadly in excitatory neurons. To examine whether SIK3 regulates structural synaptic plasticity, we analyzed dendritic spine size in the PFC excitatory

neurons of Sleepy mutant mice, exhibit marked increases in NREM sleep duration and delta power. Spine size was significantly increased in Sleepy mutant mice compared with wild-type controls. Furthermore, pharmacological inhibition of SIK3 suppressed cLTP-induced spine enlargement in primary cultures of excitatory neurons. Together, these results suggest that SIK3-dependent synaptic potentiation contributes to the regulation of NREM sleep and sleep pressure.

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Poster

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Title: Sleep-regulating kinase SIK3 promotes synaptic potentiation through suppression of RhoA activity

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Abstract: Sleep is conserved in all animals with nervous systems, but the intracellular regulatory mechanisms are largely unknown. The transition between sleep and wakefulness is driven by sleep pressure, which accumulates during wakefulness and dissipates during sleep. Recent studies suggest that the entity of sleep pressure is represented by the change of dendritic spine size (De Vivo *et al.*, 2017; Diering *et al.*, 2017; Tononi & Cirelli, 2000; Sawada *et al.*, 2024); however, the specific molecular mechanisms underlying this process remain unclear. We previously reported that the serine/threonine kinase SIK3 regulates non-rapid eye movement sleep (NREMS) delta power, an indicator of sleep pressure (Funato *et al.*, 2016; Kim *et al.*, 2022). Furthermore, we showed that constitutive activation of SIK3 enhanced phosphorylation and transcription of proteins related to synaptic potentiation (Wang *et al.*, 2018; Kim *et al.*, 2022). We therefore hypothesized that SIK3 regulates sleep pressure through synaptic potentiation.
To test the hypothesis, we conducted a series of experiments combining chemical LTP (cLTP) induction with pharmacological manipulation in primary cultured cortical neurons. First, we found that SIK3 inhibitors suppressed cLTP-induced dendritic spine enlargement. Because RhoA is known as the molecule associated with synaptic potentiation, we monitored the RhoA activity using a RhoA FRET sensor to monitor and observed that cLTP reduced RhoA activity in dendritic spine and dendritic shaft, whereas treatment with SIK3 inhibitors abolished this reduction. Furthermore, we are examining whether cLTP increases SIK3 activity using SIK3 FRET sensor. These results suggest that SIK3 promotes dendritic spine enlargement by inhibiting RhoA activity.

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Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

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Title: Chronic, partial sleep deprivation suppresses neuronal activity and increases partial pressure of tissue oxygen in the living mouse hippocampus

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Abstract: Sleep serves as a fundamental pillar of brain health, facilitating critical physiological processes such as maintenance of memory consolidation, synaptic homeostasis, mood regulation,

and metabolic waste clearance. Sleep insufficiency is a pervasive and significant health risk that remains underestimated in modern society that adversely impacts multiple physiological systems and increases risk of cardiovascular disease, obesity, diabetes, and anxiety, and cognitive decline. The hippocampus (HC), in particular, is crucial for cognitive processes such as learning and memory yet is especially vulnerable to metabolic stress compared with the neocortex. Despite its functional importance and metabolic vulnerability, investigating cellular and microvascular dynamics in the live functioning HC remains challenging due to its deep anatomical location. Here, we describe a novel cannula system that enables repeated local tissue delivery and multiphoton imaging at the same subcortical site. Leveraging this platform, we performed concurrent longitudinal neuronal activity and tissue oxygen partial pressure (pO_2) measurements in the HC of awake mice subjected to a 7-day partial sleep deprivation (SD) paradigm and a subsequent 7-day recovery period. Our results revealed a progressive decline in neuronal firing alongside a sustained elevation in tissue pO_2 during SD. Notably, neither metric returned to baseline following recovery, indicating the cumulative and enduring metabolic impairments induced by chronic sleep loss.

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Poster

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Topic: G.07. Biological Rhythms and Sleep

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Title: Acute and Chronic Sleep Deprivation Alter pre-mRNA Splicing Patterns in the Hippocampus

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Abstract: Sleep deprivation affects more than one third of the U.S. population, resulting in memory and cognitive performance deficits, and increased risk of metabolic and neurological disorders. Previous studies have shown sleep deprivation causes widespread alterations to multiple levels of gene expression from transcription to translation. Alternative mRNA splicing, particularly in neurons, enables distinct protein isoforms from a single gene and provides a mechanism for dynamic neuronal functions such as cellular signaling, neurotransmission, and synaptic plasticity. Using next-generation sequencing of bulk hippocampal tissue we have identified alterations to splicing patterns within the hippocampus of young adult male mice (3-4 months old) following either acute or repeated sleep deprivation paradigms. Animals were sleep

deprived for 5 hours per day (ZT 0 - ZT 5) using the gentle handling method of tapping the cages and gentle cage shaking. Non-sleep deprived and sleep deprived mice were sacrificed at the same time. For acute sleep deprivation (a single session), we found that there were 242 significantly different alternative splicing events from 209 genes in sleep deprived mice compared to control mice. For repeated sleep deprivation (5 days of 5 hours sleep deprivation per day), we detected 341 alternative splicing events from 282 genes. Pathway analysis shows genes alternatively spliced in acutely sleep deprived males are enriched for biological processes involved in golgi to endosome transport and regulation of histone methylation whereas chronically sleep deprived males are enriched for regulation of neuronal synaptic plasticity. Additionally, both acutely sleep deprived and chronically sleep deprived males show an enrichment of genes involved in calcium-activated cation channel activity. We verified the aberrant alternative splicing using PCR for genes of interest from both acute and chronic sleep deprivation paradigms. We found that for *Hnrnpdl*, an RNA binding protein significantly decreased in acute and chronic sleep deprivation, aberrant alternate splicing upregulates the inclusion of exon 8, “a poison exon”, to form a nonsense-mediated decay isoform thus downregulating its own transcript expression. We are currently investigating the other genes for which aberrant alternate splicing could lead to broader cellular effects. As alternate splicing is dysregulated in many neurodegenerative and neurological disorders, identifying the effects of sleep deprivation on alternate splicing may provide mechanistic insight into the mechanisms through which sleep deprivation impacts neural and cognitive function.

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Poster

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Topic: G.07. Biological Rhythms and Sleep

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Title: Repeated sleep loss drives sex-specific changes in hippocampal gene expression

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Abstract: Approximately 20% of U.S full-time workers spend more than 60 hours per week working, often resulting in long days and insufficient sleep during the week. Similarly, more

than 60% of college and high school students also experience shorter sleep during the school week. As acute sleep deprivation (SD) causes significant molecular changes resulting in neuronal dysfunction and cognitive impairments, particularly in the hippocampus, a key region for memory, we wanted to investigate the molecular impacts of repeated SD in the mouse hippocampus modeling the 5-day work week sleep deficits experienced by millions. Repeated SD consisted of 5 hours SD by gentle handling (tapping and gentle cage shaking) per day for 5 days. We analyzed the impact of repeated SD on activity and physiology using the Oxymax-CLAMS (Comprehensive Lab Animal Monitoring System) monitoring locomotor activity through infrared beam breaks, oxygen consumption, and food intake. For both males and females, repeated SD resulted in less activity during the following active period; however, there were no circadian changes in locomotor activity or other physiological parameters. At the behavioral level, mice quickly recovered from the repeated SD and exhibited similar levels of activity during both active and rest periods by the second day of recovery. To determine the impact of repeated SD on gene regulation, sleep deprived and non-sleep deprived animals were sacrificed at ZT 5 following the last period of sleep deprivation with brain tissue quickly dissected and frozen. Using an in-depth RNA sequencing approach, we found that females appeared significantly more resilient to hippocampal changes in gene expression compared to age matched males. In males, repeated sleep deprivation resulted in more than 5000 (FDR < 0.01) differentially expressed genes in the hippocampus reflecting widespread transcriptional alterations. In stark contrast, females had approximately 72 differentially expressed genes in the hippocampus. Thus, despite similar activity patterns and recovery after repeated SD in males and females, repeated SD induces significant differences in gene dysregulation between males and females. We are currently investigating the time necessary for recovery of baseline gene expression. This work highlights the differences that occur at the molecular level between males and females after SD, despite seemingly minimal differences in sleep-wake cycles and activity between the sexes after repeated SD. These molecular studies may provide insight into the links between chronic sleep deprivation and the development of neurodegenerative and dementias developed later in life.

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Poster

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Title: Using targeted high resolution spatial transcriptomics to identify subregional and cell-type specific molecular changes with acute sleep deprivation

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Abstract: Acute sleep deprivation induces significant gene dysregulation in the hippocampus, a region of the brain highly susceptible to the adverse impacts of sleep deprivation. Recent spatial transcriptomic and RNA studies have shown sleep deprivation causes subregion-specific changes in gene expression within the hippocampus. However, previous research has lacked cellular resolution. To understand the underlying mechanisms and cellular interactions through which sleep deprivation causes deficits in long-term hippocampus-dependent memory, it is necessary to define the transcriptional changes caused by sleep deprivation with cellular and subcellular resolution. To achieve this objective, we used the Xenium platform by 10X Genomics which allows spatial mapping of a targeted gene set with single cell resolution. Male mice were subjected to acute sleep deprivation consisting of 5 hours of sleep deprivation by gentle handling (tapping and gentle cage shaking). Brains were cryosectioned, slices mounted on a Xenium slide, and subsequently processed using spatial transcriptomics and a custom designed probe set. Data was initially analyzed with spectral clustering. Clusters were labeled based on anatomical region or cell-type yielding 4 anatomically labeled clusters representing the CA1, CA2, CA3 and DG of the hippocampus, and 6 cell-type specific clusters, astrocytes, endothelial cells, microglia, oligodendrocytes, and interneurons, using cell-type specific gene lists selected from marker lists with 1000 genes per cell type. Differential gene analysis was then performed for each cluster between sleep deprived and non-sleep deprived animals, followed by pathway analysis. Although there was some overlap in the genes affected by sleep deprivation across regions and cell types, we found a sizable number of unique genes in each region of the hippocampus and in different cell types, particularly in astrocytes. Notably, although many of the biological pathways appeared shared between regions or cell types including Cellular Responses to Stimuli, Development, and Gene Expression, the genes involved in those pathways differed between regions and cell types. Thus, acute sleep deprivation induces diverse responses in gene dysregulation between subregions of the hippocampus as well as in cell-type specific responses. High resolution spatial transcriptomics reveals unique cell-type specific responses that provide the basis for understanding cellular interactions occurring within a specific brain area in response to sleep deprivation, and laying the basis for understanding how sleep deprivation affects cognitive and neural function.

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Poster

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Topic: G.07. Biological Rhythms and Sleep

Title: Sleep deprivation reshapes brain-wide functional connectivity during recovery sleep and identifies the zona incerta as a potential network hub

Authors: *J. MA[1], D. SHUMIN[2], Y. YU[3];
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Abstract: Sleep deprivation induces homeostatic responses that promote recovery sleep, yet how sleep pressure reshapes large-scale brain network interactions remains incompletely understood. To investigate neural network dynamics associated with sleep homeostasis, we simultaneously recorded local field potentials from multiple sleep- and arousal-related brain regions using custom-built multichannel microwire electrodes in freely behaving mice. Mice underwent 5 h of gentle-handling sleep deprivation during the light phase (ZT0-ZT5), and neural activity during subsequent recovery sleep was compared with that observed during spontaneous sleep. Time-frequency analysis, coherence analysis, and Granger causality analysis were performed to characterize changes in oscillatory activity and functional connectivity across brain regions.Recovery sleep exhibited distinct patterns of network organization compared with spontaneous sleep. Elevated sleep pressure induced widespread changes in oscillatory dynamics and directional information flow, accompanied by reorganization of functional interactions among distributed brain regions. Connectivity analyses consistently revealed enhanced coupling involving specific subcortical structures, suggesting that these regions may serve as network hubs during homeostatic sleep responses. In particular, the zona incerta (ZI) displayed strengthened interactions with distributed sleep-related circuits across multiple analytical approaches, indicating a prominent role in coordinating brain-wide activity during recovery sleep.These findings demonstrate that sleep pressure induced by acute sleep deprivation leads to substantial reconfiguration of large-scale functional networks during subsequent recovery sleep and identify the ZI as a potential hub underlying sleep homeostasis. The results provide new insights into the circuit mechanisms by which sleep pressure shapes brain-wide communication and promotes recovery sleep.

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Poster

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Title: Basal Forebrain Npas1$^+$ Neurons as a Novel Substrate for Stress-Induced Sleep Disruptions

Authors: *T. TROPPOLI[1], J. M. MCNALLY[2], S. CHAN[4], J. T. MCKENNA[5], R. E. BROWN[3];
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Abstract: Chronic stress is a critical risk factor for psychiatric disease and sleep disruption. We recently identified a major population of basal forebrain (BF) GABAergic neurons expressing the transcription factor neuronal Per-Arnt-Sim domain 1 (NPAS1) that suppress sleep and restorative NREM cortical oscillations when chemogenetically activated (Troppoli et al., 2024; PNAS). Npas1$^+$ neurons have enhanced connectivity with stress-active amygdala neurons and mediate stress-sensitivity in rodents (Morais-Silva et al., 2023; J. Neurosci). This work uses Npas1-cre-tdTomato (C57BL/6) mice and a validated chronic multimodal stress (CMMS) model to identify the role of Npas1$^+$ neurons in stress-mediated sleep disruption. 10 days of CMMS performed early in the dark (active) phase (ZT12-16) enhanced expression of the neuronal activity proxy cFOS in BF Npas1$^+$ neurons (n=3 mice) compared to BF tissue from stress-naïve mice. Fiber photometry revealed CMMS acutely increased the frequency of photometric events in a separate cohort of mice transduced with a cre-dependent genetically encoded calcium indicator gCAMP8, further supporting the stress-sensitivity of Npas1$^+$ neurons. CMMS reduced wakefulness and increased the proportion of time spent in NREM sleep, especially during the subsequent dark period ($p<0.05$; n=11). Slow-wave (0-1.5Hz, $p<0.05$) and delta power activity (1.5-4Hz, $p<0.01$), oscillatory markers of NREM sleep quality, were reduced, while delta and theta (4-9Hz; $p<0.05$) powers during wakefulness, markers of sleep pressure, were enhanced. A subset (n=6) of these mice was transduced with a cre-dependent hM4Di chemogenetic construct to facilitate inhibition of Npas1$^+$ neurons post-CMMS with clozapine-n-oxide (CNO). Injections (i.p.) were given early into the light (ZT2) and dark (ZT14) cycles. Our previous work using CNO to activate BF Npas1$^+$ neurons found an effect persisting for approximately 3 hours, and so analysis was constrained to this period. Compared to saline vehicle, CNO given during the dark cycle tended enhanced the amount of NREM sleep ($p=0.13$) and entries into NREM sleep ($p<0.05$), as well as NREM slow wave oscillatory activity ($p=0.19$) following CMMS, indicative of deeper sleep. Furthermore, slow ($p=0.09$) and delta ($p=0.08$) activity, oscillatory markers of sleep pressure during wakefulness tended to be reduced, possibly in response to higher-quality NREM sleep. Furthermore, post-stress deficits in sucrose preference, a behavioral proxy of anhedonia, were restored following CNO administration. Together, these data suggest BF Npas1$^+$ cells are a novel neurobiological substrate linking chronic stress to sleep and psychiatric disorders.

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Poster

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Program #/Poster #: PSTR279.18/GG19

Topic: G.07. Biological Rhythms and Sleep

Title: Epigenomic signatures of sleep-need accumulation in cortical excitatory neurons

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Abstract: Accumulating evidence suggests that cortical synaptic strength increases during wakefulness and decreases during sleep, reflecting sleep pressure. We previously demonstrated a causal link between excitatory synaptic strength in the prefrontal cortex (PFC) and both the amount and depth of sleep (Sawada et al., 2024). However, the mechanisms underlying synaptic upregulation during wakefulness remain unclear. Epigenomic mechanisms, including histone modifications, are dynamically regulated in response to external stimuli and can encode cellular history. Also, it is known to contribute to the maintenance of synaptic strength in cortical excitatory neurons over hours to days. In this study, we first profiled more than ten histone marks using CUT&Tag to examine their changes in response to sleep-need accumulation in excitatory neurons across multiple brain regions. By combining these datasets with publicly available ATAC-seq and RNA-seq data, we identified epigenomic signatures associated with accumulated sleep need and we obtained several candidate molecules for functional validation. We next performed an in vitro validation of these candidates by combining siRNA-mediated mRNA knockdown with a multielectrode array recording of sleep like up-down network activity and live-cell imaging of dendritic spines. This approach enables us to identify multiple candidate molecules involved in the regulation of synaptic plasticity and neural activity.Finally, to determine the effects of these candidates on sleep phenotypes at the individual level, we performed somatic knockout in CaMKII-positive neurons in the adult brain. Overall, our findings suggest that nuclear dynamics, including histone modifications, modulate synaptic dynamics in cortical excitatory neurons and thereby contribute to the regulation of sleep pressure.

Disclosures: S. Nomura: None. **H. Ono:** None. **C. Shimizu:** None. **K. Yoshida:** None. **Y. Iino:** None. **S. Shi:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.19/GG20

Topic: G.07. Biological Rhythms and Sleep

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Title: Long non coding RNA Cerox1 regulates memory impairment by targeting energy metabolism after sleep deprivation

Authors: K. RAVICHANDRAN[1], P. KISKU[1], L. NINGCHANGMI[1], S. STRACK[2], E. T. ABEL[3], ***S. BANERJEE**[1];
[1]BRIC Natl. Brain Res. Ctr., Manesar, India; [2]Univ. Iowa, Iowa City, IA; [3]Univ. of Iowa, Iowa City, IA

Abstract: Memory storage is often disrupted by sleep loss. Emerging studies have demonstrated that sleep-wake cycles define the energy expenditure in neurons. However, our understanding is limited regarding how sleep regulates the ATP level and how disruption of this regulatory process causes memory deficit. So far, the phosphorylation of adenosine monophosphate-dependent kinase (AMPK), a metabolic sensor of energy state, and expression of multiple components of the electron transport chain (ETC) have been shown to regulate energy metabolism after sleep deprivation (SD). Building on findings that disrupted AMPK signalling impairs protein synthesis after SD, this study examined the role of regulatory RNAs in SD-induced memory deficits. Among diverse classes of regulatory RNAs, the study focused on long non-coding RNAs (lncRNAs) that are pivotally positioned to govern gene expression mechanisms with spatial and temporal resolution. A comparative analysis of hippocampal transcriptome after sleep deprivation and synapse-localized lncRNAs has identified a subset of lncRNAs that are regulated by SD. Among these, we have characterized the role of Cerox1 that is downregulated after 5 hours of sleep deprivation and a rebound sleep for 2.5 hours after SD reversed its expression. We observed that the Cerox1 targets transcripts encoding subunit of complex I of ETC via miRNA -dependent mechanism. SD or knockdown of Cerox1 reduces the activity of complex I of ETC and its overexpression restores the activity. Consistent with this observation, we have detected a reduction in ATP level after SD and the ATP level was restored after the overexpression of Cerox1. Notably, overexpressing Cerox1 with intact miRNA binding sites reversed SD-induced memory impairment and reduction in the ATP level, whereas a variant lacking these sites did not. Our study further revealed that sleep deprivation (SD) lowers the levels of NDUFS1 and NDUFS3, which are vital subunits of mitochondrial Complex I. We were able to reverse this decline by overexpressing Cerox1, but only when it retained its miRNA binding sites. This is because Cerox1 shares common miRNA binding targets with both NDUFS1 and NDUFS3, allowing it to act as a molecular decoy. Consequently, SD appears to impair memory by disrupting Cerox1's decoy activity, which compromises the energy (ATP) levels in the dorsal hippocampus needed for memory storage. Together, these insights uncover a

new long non-coding RNA -dependent mechanism that links disruption of energy production to sleep loss-induced memory deficits.

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Poster

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Program #/Poster #: PSTR279.20/GG21

Topic: G.07. Biological Rhythms and Sleep

Title: mGluR5-PKA Signaling in a Cellular Model of Sleep Need

Authors: *M. YE[1], G. H. DIERING[2];
[1]Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [2]Cell Biol. and Physiol., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: Nearly all animals sleep, but the cellular mechanisms that regulate sleep need remain poorly understood. In mammals, sleep need is biochemically encoded at the synapse. Here we 1) tracked sleep need at mouse cortical synapses via sleep deprivation (SD) and subsequent recovery sleep (RS) in vivo, and 2) modelled these processes in rodent primary cortical neurons in vitro. We show that sleep need in vivo is biochemically encoded by a biphasic pattern of synaptic cAMP-dependent protein kinase A (PKA). During SD, synaptic PKA activity is elevated and GluA1-containing AMPA receptor accumulates at the synapse. During RS, synaptic PKA activity decreases and GluA1 is removed from the synapse, consistent with homeostatic synaptic downscaling (HSD). Pharmacologically induced HSD in vitro recapitulates the phosphorylation dynamics of sleep need in vivo. Phosphoproteomics in vitro identified PKA as the dominant kinase driving the biphasic process, and revealed a subsequent wave of extensive proteome remodeling, suggesting PKA activation and subsequent suppression initiate large-scale proteome reconfiguration and broader molecular adaptation. This biphasic pattern of PKA is regulated by metabotropic glutamate receptor 5 (mGluR5) pathway, a human sleep gene involved in human response to SD. These results provide a novel cellular model for how mGluR5-PKA regulates cortical synaptic adaptations to prolonged activity, and its implications for the accumulation and resolution of sleep need.

Disclosures: M. Ye: None. **G.H. Diering:** None.

Poster

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Title: The NALCN channel complex is necessary for stabilizing sleep in Caenorhabditis elegans

Authors: *T. KAMIJO[1], S. MIYAZAKI[1,2], Y. HAYASHI[1,2];
[1]Dept. of Biol. Sciences, Grad. Sch. of Sci., The Univ. of Tokyo, Bunkyo-ku, Tokyo, Japan;
[2]Intl. Inst. for Integrative Sleep Med. (WPI-IIIS), Tsukuba Inst. for Advanced Res. (TIAR), Univ. of Tsukuba, Tsukuba, Ibaraki, Japan

Abstract: Sleep is a fundamental physiological state that is widely conserved across diverse animal species. *Caenorhabditis elegans* exhibits developmentally timed sleep (DTS) and stress-induced sleep (SIS), which meet the behavioral definition of sleep and are regulated by molecular mechanisms shared with other animals. Here, we studied the sleep-regulating functions of UNC-80, which forms a complex with NCA-1 and NCA-2 (hereafter collectively referred to as NCA), and UNC-79. We found that the *unc-80* loss-of-function (lf) mutants experienced lower quiescence and a more fragmented and longer DTS than the wild type. The *unc-80(lf)* mutants also showed lower quiescence during SIS immediately after heat stress, and fragmented SIS. After that, however, quiescence remained higher for a longer time, resulting in a higher total quiescence than observed in the wild type. Similar sleep defects were observed in *nca(lf)* and *unc-79(lf)* mutants, indicating that these genes have common functions in sleep regulation. *nca-1* gain-of-function (gf) mutants showed lower quiescence during DTS and SIS, suggesting that precise tuning of NALCN channel activity within an appropriate dynamic range might be critical for sleep regulation. Deprivation of SIS immediately after heat stress in the wild type resulted in a sleep pattern similar to that of the *unc-80(lf)* mutants, suggesting that sleep immediately after stress might be essential and thus is under strong homeostatic regulation and that the prolonged DTS and SIS of the *unc-80(lf)* mutants might be rebound sleep. Finally, *nca(lf)* and *nca-1(gf)* mutants exhibited lower quiescence specifically during the early phase following severe heat stress and showed markedly shortened survival length. These results suggests that early period of sleep is important for survival. Together, our findings demonstrate that NCA, UNC-79, and UNC-80 are necessary for stabilizing sleep and suggest the importance of the early period of sleep.

Disclosures: T. Kamijo: None. **S. Miyazaki:** None. **Y. Hayashi:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH NIGMS (R35GM150658)

Title: Stress-induced sleep regulation by neuropeptide NLP-67 in C. elegans

Authors: *V. RAJ[1], R. LEMON[1], L. GOLINELLI[2], I. BEETS[2], H. WANG[1];
[1]Univ. of Wisconsin, Madison, WI; [2]KU Leuven, Leuven, Belgium

Abstract: Sleep is a highly conserved physiological process across invertebrates and vertebrates. *C. elegans* enters a sleep state when the animals encounter external stressors, such as heat, UV, and pathogens. In *C. elegans,* the stress-induced sleep (SIS) is characterized by cessation of feeding, body movements as well as reduced sensory responsiveness. SIS is primarily mediated by the activation of epidermal growth factor (EGF) signalling through the EGF receptor (EGFR) in the ALA neuron. However, the downstream molecular pathways mediating this response remain incompletely understood. Here, through an unbiased forward genetic screen, we identified the *neuropeptide-like protein* NLP-67 as a novel sleep signal from the ALA neuron. We demonstrate that NLP-67 is expressed in and functions within the ALA neuron and that its conditional overexpression is sufficient to promote sleep. We identified NPR-28, an allatostatin C-type GPCR, as the receptor for NLP-67. NPR-28 is expressed in neurons, intestine, and pharyngeal muscles. We showed that NLP-67 activates NPR-28 to mediate sleep by silencing NPR-28-expressing neurons via inhibitory G-protein signalling. Together, our findings demonstrate a novel neuropeptide-GPCR signalling downstream of EGF that enables a single neuroendocrine neuron to regulate SIS. This neuropeptide-GPCR interaction and the underlying molecular mechanisms will advance our understanding of sleep regulation in animals.

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Poster

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Topic: G.07. Biological Rhythms and Sleep

Support: JP25KJ0665
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JP24zf0127011

Title: Forward genetics in Caenorhabditis elegans identifies conserved regulators of sleep

Authors: *Y. SAKAGUCHI[1,2], T. KAWANO[2], M. YANAGISAWA[2,3], Y. HAYASHI[2,4]; [1]Tsukuba Univ., Ibaraki/Tsukuba, Japan; [2]Intl. Inst. for Integrative Sleep Med. (WPI-IIIS), Tsukuba Univ., Tsukuba, Japan; [3]Dept. of Mol. Genet., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [4]Dept. of Biol. Sci., Univ. of Tokyo, Tokyo, Japan

Abstract: Sleep is a widespread phenomenon observed across diverse animal phyla, ranging from Vertebrata to Cnidaria such as jellyfish, an ancient metazoan phylum lacking a central nervous system. These findings suggest that the phylogenetic origins of sleep predate the emergence of the central nervous system. However, the overall molecular mechanisms underlying the regulation of sleep and wakefulness have yet to be fully elucidated. For example, although rare familial cases of natural short sleepers with extremely short sleep duration have been reported in humans, only a limited number of causative genes have been identified to date. We previously found that the molecular mechanisms regulating sleep are highly conserved across vertebrates (e.g., mammals) and invertebrates (e.g., nematodes). Therefore, the genetically tractable nematode *Caenorhabditis elegans* provides a powerful model for elucidating evolutionarily conserved mechanisms of sleep regulation. Using *C. elegans*, we employed a phenotype-driven forward genetic screen to isolate mutant strains exhibiting a severe short-sleep phenotype. Further analyses of these strains demonstrated that mutants lacking several genes in the peptide processing pathway displayed a short-sleep phenotype. Peptide processing pathways are highly conserved across phyla, and peptide signaling plays an important role among the primitive components of cell-cell communication systems, such as neuroendocrine systems. These results suggest that peptide maturation contributes to the regulation of sleep and wakefulness. We are currently investigating whether these mechanisms are conserved in mammals by analyzing homologous mutants in mice. By uncovering the role of peptide maturation in sleep-wake transitions, our study has the potential to clarify the underlying conserved molecular mechanism of sleep-wake regulation and to identify new therapeutic targets for treating sleep disorders.

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Poster

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Program #/Poster #: PSTR279.24/HH1

Topic: G.07. Biological Rhythms and Sleep

Support: NSF Grant IOS-2445004
NSF Grant IOS-1845020

Title: A simple circuit composed of a complex signaling network underlies sleep in C. elegans

Authors: R. VEMULA, *M. NELSON;
St. Joseph's Univ., Philadelphia, PA

Abstract: Sleep is highly conserved at the genetic level, yet our understanding of the circuit mechanisms underlying sleep is far from complete. Stress-induced sleep (SIS) of Caenorhabditis elegans is a simple model for the mechanistic dissection of sleep. SIS is largely controlled by only two interneurons (ALA and RIS), within a compact and genetically tractable 302-celled nervous system. We examined numerous genes encoding neuropeptides, G protein-coupled receptors, a two-pore potassium channel, and glutamate signaling components, and identified multiple genes required for sleep maintenance (i.e., sleep quantity) and/or the precise timing of sleep initiation. In particular, we identified crucial roles for a conserved ionotropic glutamate receptor glr-5, and a neuropeptide receptor, npr-38. Loss of function of both glr-5 and npr-38 reduces sleep, and overexpression of npr-38 causes a striking shift in the timing of sleep, initiating earlier. Using cell-specific rescue, we find that glr-5 functions in 3 interneurons, which include the RIS, that are highly connected by gap junctions and chemical synapses, while npr-38 functions in a sensory neuron (ADL) (Howe et al. 2026. Genetics; Le et al. 2023. Current Biology), that is presynaptic to the ALA and the aforementioned three-celled circuit, which includes RIS. We propose that these five cells form a central circuit underlying sleep timing and maintenance.
To better understand the mechanisms of this circuit, we have been using an optogenetic and gene discovery approach. First, using the split-Gal bipartite system (Wang et al. 2018, PNAS) to drive expression of the red-light-activated sodium channel Chrimson in each cell individually. We then measure sleep following neuron activation at different time points. Second, we performed RNA sequencing in wild-type, npr-38 loss-of-function, and npr-38 overexpressing animals, prior to and at various time points after sleep initiation. Using this approach, we are characterizing the roles of each individual neuron of this 5-celled circuit during sleep, and have identified numerous differentially expressed genes involved in neurotransmission, the immune response, and gene regulation.

Disclosures: R. Vemula: None. **M. Nelson:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH/NINDS R01 Award NS130108
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Title: Testing for direct links between sleep and known synaptic homeostasis maintenance factors

Authors: *E. FONTENOY, C. FRANK;
Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: To keep behaviors controlled, nervous system outputs need to stay within physiological bounds. At the levels of neurons, synapses, or circuits, this means that homeostatic forms of regulation are needed. Homeostatic regulation has been intensively studied in *Drosophila melanogaster*. Our lab and others identified factors that are critical for the maintenance of homeostasis at synapses. We hypothesized that some of these factors might play roles in complex behavioral processes where stability is needed. The idea of homeostatic regulation has been extended to specific behaviors like sleep. The synaptic homeostasis hypothesis (SHY) in the sleep field posits that sleep is used as an off-line period to restore the brain's capacity for plasticity that is needed during wakefulness. If the general concept of SHY is correct, perturbations that disrupt sleep would affect synaptic homeostasis, and likewise, disruptions to synaptic homeostasis would also affect sleep. Previous research has shown that disruptions in a subset of canonical sleep genes can also cause disruptions to synaptic homeostasis. For our current work, we used *Drosophila* Activity Monitors to test for abnormal sleep phenotypes in adult *Drosophila* with loss-of-function mutations in the synaptic homeostasis maintenance factors. When compared to wild-type, disruptions in a subset of the synaptic homeostasis genes identified in *Drosophila* showed changes to the amount of sleep. The most common changes seen were differences in the amount of daytime sleep, with the nighttime sleep unaffected. In this category the factors that showed an increase in the sleep included loss-of-function conditions in signaling factors like Ephexin (Rho-type GEF), Eph receptor, and S6 Kinase. By contrast, loss-of-function conditions that showed decreased sleep included the ryanodine receptor, Src64B (Src family kinase), Stumps (adaptor), Gαq, and Arl8. Additionally, we found some *Drosophila* mutant conditions showing changes to the nighttime sleep, with the daytime sleep unaffected. These included a chromosomal deletion affecting both Pyramus and Thisbe (FGF ligands), which has increased nighttime sleep, and IMD (innate immune molecule), which has decreased nighttime sleep. A final category included loss-of-function conditions that showed changes to the total sleep. These include Csp (cystine string protein), which has an increase, and Smn (Survival motor neuron), which has a decrease. We are currently analyzing these phenotypic groups and determining how they work together to regulate sleep in *Drosophila*. A major long-term goal is pinpointing the tissues and circuits where each factor acts to control sleep behavior.

Disclosures: E. Fontenoy: None. **C. Frank:** None.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR279.26/HH3

Topic: G.07. Biological Rhythms and Sleep

Title: Impact of mechanical rocking on sleep in Alzheimer's Disease model Drosophila

Authors: *M. AMKEIE[1], R. GUERRIERO[2];
[1]George Mason Univ., Ashburn, VA; [2]Interdisciplinary Program of Neurosci., George Mason Univ., Fairfax, VA

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by neuronal loss, tau and amyloid-beta protein accumulation, and behavioral changes, including disrupted sleep. Changes in sleep patterns often appear before severe cognitive symptoms develop and this sleep disruption may contribute to disease progression. Previous studies in Drosophila models have shown that increasing sleep, through pharmacological approaches, can improve memory and reduce AD-related pathology, likely due to waste clearance that takes place during sleep, which may influence toxic protein buildup. However, it remains unclear whether these benefits result from increased sleep itself or from the drugs used to induce sleep. Pharmacological treatments can directly affect behavior and cognitive function, making it difficult to separate the effects of sleep alone. As a result, the effects of increasing sleep through non-pharmacological methods in Alzheimer's disease models remain poorly understood. This study examines whether increasing sleep using mechanical rocking may improve sleep and cognitive outcomes, including short-term and long-term memory, in Drosophila models of Alzheimer's disease. Drosophila lines expressing AD were generated through the UAS-Gal4 system. Flies expressing tau and amyloid-beta protein were monitored using Drosophila Activity Monitors (DAM2), which detect movement through infrared light beam crossings. To increase sleep without pharmacological intervention, monitors were placed on a shaker plate that provided gentle rocking movements. We confirmed that after rocking, AD flies show decreased homeostatic need for sleep due to shorter sleep duration, shorter sleep bouts, and more fragmented sleep. Sex differences were also found with males generally showing longer sleep duration during early circadian day than females. These findings indicate that tau and amyloid-beta proteins affect the sleep homeostat differently depending on genotype and sex, but also that our rocking does impact sleep need in AD flies. Next steps include measuring AD symptomology, with short-term memory measured using Aversive Phototaxic Suppression (APS) and long-term memory measured using olfactory learning. Understanding how sleep-need impacts the progression of Alzheimer's disease may help identify early behavioral changes associated with disease progression and cognitive decline. This study may provide insight into whether improving sleep could be used as a non-drug approach to support cognitive function and reduce symptoms associated with Alzheimer's disease.

Disclosures: M. Amkeie: None. **R. Guerriero:** A. Employment/Salary (full or part-time):; George Mason University.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH/NINDS Grant R15NS101692-02A1
Skidmore College's Faculty-Student Summer Research Program

Title: Characterizing Sleep-Regulating sNPF Neurons in the Ventral Nerve Cord of Drosophila melanogaster

Authors: *R. MOI[1], A. IRELAND[1], J. STUART[1], D. POSSIDENTE[1], M. BENNETT[3], A. M. DACKS[4], C. G. VECSEY[2];
[2]Neurosci. Program, [1]Skidmore Col., Saratoga Springs, NY; [4]Dept. of Biol., [3]West Virginia Univ., Morgantown, WV

Abstract: Sleep is a fundamental biological process, modulated by numerous factors. It has become clear that neuropeptides play a critical role in regulating sleep. However, the mechanisms underlying their function remain largely unknown. One such neuropeptide is short neuropeptide F (sNPF), a precursor to four neuropeptides that bind G protein-coupled receptors homologous to the mammalian neuropeptide Y (NPY) receptor. Optogenetic activation of sNPF-expressing neurons has been shown to dramatically promote sleep in *Drosophila melanogaster*. However, sNPF is widely expressed in the *Drosophila* nervous system, and it is unknown which sNPF neurons contribute to this effect. When sNPF neurons in the ventral nerve cord (VNC)—the fly analog of the spinal cord—are excluded from optogenetic stimulation using tsh-GAL80, this sleep-promoting effect is significantly attenuated, implicating VNC sNPF neurons as key mediators of this behavior. To better characterize this circuitry, we quantified the neurons silenced by tsh-GAL80 and examined their co-expression of other neurotransmitters. We observed reductions approaching 70% in Chrimson expression within sNPF neuron clusters in the VNC, specifically in clusters in the medulla and posterior to T1, T2, T3, with the effect becoming increasingly prominent in more posterior segments. Within sNPF-expressing neuron clusters posterior to T2 and T3, sNPF was found to colocalize with acetylcholine (ACh) and, more prominently, GABA, demonstrating co-expression of both excitatory and inhibitory small-molecule transmitters alongside the neuropeptide sNPF. It is still unknown which of these clusters is key for sleep promotion, and how the co-release of sNPF alongside ACh and GABA is integrated postsynaptically. Future experiments will assess the acute behavioral effects of optogenetically activating sNPF neurons in both larvae and adults under tsh-GAL80 suppression. Additionally, targeted activation of VNC sNPF neurons in isolation will further determine whether this population is sufficient to induce sleep. These findings will shed light on the ways neuropeptides and neurotransmitters work together to regulate sleep. The localization of these high-impact clusters to the VNC rather than the brain raises questions about how nervous system regions collaborate to regulate sleep, underscoring the need for a more integrative approach to studying sleep circuitry.

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Poster

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Program #/Poster #: PSTR279.28/HH5

Topic: G.07. Biological Rhythms and Sleep

Title: The Role of Pituitary Homeobox 1 (Ptx1) in Sleep Regulation and Dopaminergic Signaling in Drosophila melanogaster

Authors: D. CHORDIA, *R. GUERRIERO;
George Mason Univ., Fairfax, VA

Abstract: Sleep is a relatively under researched process regulated by complex genetic networks. The specific role of Pituitary homeobox 1 (*Ptx1*) - a transcription factor essential for developmental patterning - remains poorly understood in sleep, although previous research in mouse knockouts show fragmented and decreased sleep. We followed this up to determine if knockdown of *Ptx1* in specific neural circuits can alter sleep architecture and modulate arousal in *Drosophila melanogaster*. With the UAS-GAL4 system, virgin female and males were monitored for sleep behavior using the *Drosophila* Activity Monitoring (DAM2) system, with sleep defined as periods of >5 minutes of inactivity. Initial results from the pan-neuronal knockdown using *elav-GAL4* and *TRIP* RNAi showed significant alterations in sleep duration and consolidation, with both sexes sleeping similarly ($p=0.2066$) and maintaining high sleep levels ($p<0.0001$), suggesting that global loss masks localized, hyper-active phenotypes. This process was repeated for flies with *Ptx1* depletion specifically within dopaminergic neurons via *TH-GAL4* to assess the impact on arousal-promoting circuits. In the dopaminergic-specific lines, we observed a massive divergence between sexes ($p<0.0001$); while males maintained robust midday sleep peaks and high nighttime sleep duration, females exhibited significantly reduced sleep and erratic activity patterns throughout the light/dark cycle. Interestingly, comparisons across knockdowns indicated that pan-neuronal knockdown resulted in higher sleep consolidation in females than the dopamine-specific knockdown. These findings support the hypothesis that while *Ptx1* loss in dopaminergic neurons promotes wakefulness, its absence in other neuronal populations may initiate a compensatory mechanism that partially mitigates this effect. In contrast, male sleep patterns remained relatively consistent across both drivers, indicating that the influence of *Ptx1* on male sleep is primarily mediated through dopaminergic signaling. These findings provide preliminary evidence that *Ptx1* serves as a novel, sex-specific regulator of sleep architecture. Future directions include analyzing the effects of *Ptx1* knockdown within GABAergic circuits to further delineate the inhibitory and excitatory networks involved in this phenotype.

Disclosures: D. Chordia: None. **R. Guerriero:** A. Employment/Salary (full or part-time):; George Mason University.

Poster

PSTR279: Plasticity and Regulation of Sleep and Sleep Deprivation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: G.07. Biological Rhythms and Sleep

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Title: NaPi-III Phosphate-Flux Recovery Couples Circadian Timing to Sleep Homeostasis in Drosophila

Authors: *A. FUJIMAKI[1,2], M. INDEN[1], M. TABUCHI[2];
[1]Gifu Pharmaceut. Univ., Gifu, Japan; [2]Dept. of Neurosciences, Case Western Reserve Univ. Sch. of Med., Cleveland, OH

Abstract: Sleep is governed by circadian timing and homeostatic sleep drive, but the neuronal state variable that carries wake history while preserving circadian phase remains unresolved. We identified a NaPi-III-dependent phosphate-flux recovery mechanism in *Drosophila* DN1p circadian clock neurons linking these processes. We performed simultaneous dual quadruple electrophysiological recordings and applied an Ornstein-Uhlenbeck model to quantify membrane potential resilience. We found that the phosphate-dependent restoring coefficient drives voltage back to a phase-specific baseline after stochastic ion-driven fluctuations. In controls, DN1p neurons maintained circadian phase-specific recovery set points. Prolonged wakefulness selectively decreased phosphate-evoked current and resilience relative to the phase-matched set point, whereas recovery sleep restored both. We found that DN1p-specific RNAi knockdown of the *SLC20A2* ortholog NaPi-III weakened resilience, in addition to canonical hyperexcitability, destabilized spike timing, impaired synaptic recovery and plasticity, and produced reduced daytime sleep, longer sleep latency, and sleep fragmentation. Bidirectional manipulations established causality: maintaining NaPi-III-dependent phosphate-flux recovery during enforced wakefulness attenuated rebound sleep, whereas blocking recovery during behavioral sleep prevented normal discharge of sleep pressure. Mechanistically, we identified that NaPi-III-dependent recovery required a Futsch/MAP1B light-chain-dependent presynaptic mitochondrial microdomain that deteriorates with aging. These findings provide a cellular implementation of the two-process model in which circadian phase defines the phosphate-flux recovery set point, wakefulness consumes ion-metabolic resilience, and sleep restores it. Thus, we propose that sleep pressure can be read out as a reversible loss of NaPi-III-dependent membrane resilience in circadian sleep-regulatory neurons.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Program #/Poster #: PSTR280.01/HH7

Topic: I.03. Decision Making

Support: NIMH 129320
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NIDA 051598

Title: Dissociable contributions of sex and estrous to reward-guided decision-making

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Abstract: Introduction: The ability to adapt in response to environmental uncertainty is a critical survival mechanism. Sex-dependent differences in adaptive decision making have been previously observed, but the underlying mechanisms have not been thoroughly explored. While it is known that estrous stage and cycling hormones influence reward-related brain functions, their contributions to adaptive decision making are unknown. The current study examined sex differences and the involvement of estrous in adaptive reward-guided decision making.
Methods: Decision-making functions were assessed in adult female and male Long Evans rats using a three-choice probabilistic reversal learning task. Rats were trained on a volatile schedule of reinforcement in which the reward probabilities assigned to the three options changed frequently. Rats were also tested under a stable schedule of reinforcement, in which a single reversal occurred in each session. Vaginal cells were collected in female rats twice per week to determine estrous stage.
Results: We found that female rats completed fewer trials, achieved fewer reversals on the volatile schedule, and performed worse following a reversal compared to male rats. These differences were largely explained by disruptions in reward-guided decision-making in female rats, as the probability that rats would repeat unrewarded actions was similar across sexes. Unlike our observations between the sexes, we did not find estrous-based differences in the number of reversals completed on the volatile schedule of reinforcement. In the stable schedule, learning during acquisition was comparable across estrous stages. Reversal performance, however, was found to be worse during diestrus and proestrus compared to metestrus and estrus. This estrous-mediated difference was also driven by deficits in reward-guided decision making. Nevertheless, reversal performance was significantly lower in female rats across all estrous phases compared to males, suggesting that hormonal fluctuations during estrous do not fully account for the robust sex differences observed here.
Conclusions: We found robust sex differences in reward-guided decision making across diverse schedules of reinforcement that were driven by variations in positive feedback-dependent learning. Although estrous-based deficits after a reversal are related to the same decision-making strategies, they do not fully explain this sexual dimorphism and may be coinciding with differences in non-cycling hormones or neural circuitry. Ongoing work is looking at the role of

hormones during development, as well as circuit-level mechanisms that could underlie these behaviors.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Topic: I.03. Decision Making

Support: NIDA T32DA043469
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Title: Individual differences in cue responsivity are associated with distinct feedback-guided decision-making strategies

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Abstract: Adaptive decision-making requires individuals to continuously update behavior in response to changing environmental contingencies. However, reward-predictive cues can acquire motivational value and influence behavior, potentially shaping how individuals respond to feedback and adapt to changing environments. Importantly, individuals differ in the extent to which reward-predictive cues acquire incentive motivational value, resulting in variability in the degree to which cues guide behavior and influence decision-making. Understanding the factors that contribute to individual differences in cognitive flexibility and cue-guided behavior is critical for identifying mechanisms that promote adaptive decision making. Therefore, it was hypothesized that individuals exhibiting greater cue responsivity would display distinct feedback-guided learning strategies during adaptive decision-making, characterized by great reliance on positive feedback and reduced sensitivity to negative feedback. To test this hypothesis, individual differences in cue responsivity were assessed using the Pavlovian conditioned approach (PavCA) task in adult male and female rats. Following PavCA testing, animals were subsequently trained on a three-choice probabilistic reversal learning task. Adaptive decision-making was evaluated under both volatile and stable reward environments. In the volatile condition, reward contingencies were reversed multiple times within a session, requiring continuous behavioral updating. In the stable condition, animals completed a single reversal following acquisition of the initial contingency. Preliminary analyses revealed no significant relationship between degree of cue responsivity and overall task performance,

including reversals completed across volatile reward conditions. However, individuals exhibiting higher levels of cue responsivity showed a trend toward persistence following nonreward in the Stable High condition, suggesting that negative outcomes exerted less influence on subsequent choice behavior. These findings suggest that cue responsivity may influence how feedback is incorporated during adaptive decision-making, promoting distinct feedback-guided learning strategies rather than broad differences in cognitive flexibility.

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Poster

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Title: Neural basis of contrafreeloading in rats: the anterior cingulate cortex contributes to the preference for effortful reward acquisition

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Abstract: Animals tend to expend effort to obtain food even when an equivalent reward is freely available. For example, rats prefer the effortful option of pressing a lever to acquire food over simply eating it from a dish. This counterintuitive behavior is known as contrafreeloading. Contrafreeloading has been observed in a wide range of species and assumed to share a common neural mechanism. Although contrafreeloading is believed to arise from animals' innate tendency to prefer earning rewards, there are alternative accounts, such as the idea that it is driven by the avoidance of boredom. Another possibility is that rats simply prefer effortful action per se due to secondary reinforcement. To address these possibilities, we established a novel experimental system, in which rats were allowed to freely choose effortful rewards, free rewards, and effort alone. Using this system, we observed contrafreeloading behavior independent of boredom and secondary reinforcement. To investigate the neural basis of contrafreeloading, we inhibited neural activity in targeted brain regions by injecting muscimol, a $GABA_A$ receptor

agonist. We found that inhibition of the anterior cingulate cortex (ACC) impaired contrafreeloading without affecting locomotion or food intake. While the ACC is known as a hub for calculating cost and benefit during decision-making, our findings suggest that this region assigns value to the effortful process of reward acquisition itself, thereby driving the contrafreeloading behavior. Decision-making in contrafreeloading is a complex process consisting of multiple elements, such as effort calculation and reward value comparison. Therefore, it requires temporally precise processing of neural information at each behavioral stage. Here, we conducted electrophysiological recordings in the ACC and related brain regions of rats performing the task. This allowed us to observe neural activity with high temporal resolution at specific behavioral time points and examine the neural mechanisms underlying information processing. Contrafreeloading is a peculiar phenomenon that seemingly defies traditional cost-benefit principles, yet it is broadly conserved across species. Thus, revealing the neural basis of contrafreeloading could lead to the discovery of a novel and universal principle of decision-making. Moreover, extreme contrafreeloading behavior can be regarded as a state of exerting excessive effort for rewards and is utilized as a model for psychiatric disorders such as addiction and obsessive-compulsive disorder. Therefore, identifying its neural mechanisms also contributes to understanding the pathology of these disorders.

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Poster

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Title: Causal contribution and neural correlate of parafascicular nucleus in perceptual decision-making

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Abstract: *Objective:* The parafascicular nucleus (PF), an intralaminar thalamic nucleus, is extensively connected with the prefrontal cortex, basal ganglia, and superior colliculus, all of which contribute causally to decision-making behavior. While PF has been implicated in motor initiation, attention, and behavioral flexibility, its role in perceptual decision-making and the underlying neural mechanisms remain unclear. *Methods:* Mice performed a two-alternative forced-choice visual motion discrimination task, with a basic version and a reward-context

variant. In this variant, reward magnitude was asymmetrically assigned across blocks such that correct choices to one side yielded larger reward than the other. Block switches were uncued, requiring animals to integrate sensory evidence with reward context to guide decisions. We used optogenetic and chemogenetic manipulations together with high-density Neuropixels recordings to examine underlying neural mechanisms. *Results:* In the basic task, unilateral PF inactivation induced a contralateral bias ($p = 0.02$, Wilcoxon signed-rank test, $n = 9$ mice). This effect was restricted to the stimulus/decision window and was most pronounced during low-coherence trials, indicating a contribution of PF to perceptual decision processes beyond motor execution. In the asymmetric reward task, unilateral PF inhibition reduced the difference in bias between right-more and left-more reward blocks (beta = -12.2, $p = 0.035$, linear mixed model, $n = 54$ sessions from 9 NpHR mice, $n = 36$ sessions from 6 control mice). PF inhibition also selectively slowed behavioral updating following switches from right-more to left-more blocks ($p = 0.04$, two-way ANOVA with mixed design; NpHR: $n = 9$ mice, control: $n = 6$ mice), with no significant effect in the opposite switching direction. This effect was restricted to low-coherence trials (20% and 40%; $p = 0.035$, two-way ANOVA with mixed design) and was not significant during high-coherence trials (60% and 100%; $p = 0.14$, two-way ANOVA with mixed design), suggesting that PF supports the use of reward context when sensory evidence is weak. Neuropixels recordings in the basic task revealed that a minority of PF neurons encoded stimulus direction, whereas a larger fraction exhibited significant choice preference. Both stimulus and choice preference were stronger in easy than in difficult trials, indicating that PF activity encodes evidence-dependent decision-related signals. Ongoing experiments investigate how PF neurons integrate sensory and reward context information to support adaptive decision-making.

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Poster

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Topic: I.03. Decision Making

Support: R01AA021505
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U01AA025932

Title: Direct-pathway medium spiny neuron-driven acetylcholine pause-rebound dynamics encode reward-predictive salience and gate dopamine release during instrumental learning

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Abstract: Instrumental learning links actions to outcomes, but how dorsomedial striatal circuits coordinate local acetylcholine (ACh) and dopamine (DA) signals to support this process remains unclear. We combined genetically encoded ACh and DA sensors, fiber photometry, ex vivo electrophysiology, and in vivo optogenetics in mice to define how direct-pathway medium spiny neurons (dMSNs) interact with neuromodulator dynamics during fixed-ratio learning. ACh and DA were both engaged during learning but carried distinct information. DA primarily tracked reward delivery, whereas dMSN activity and a biphasic ACh pause-rebound emerged at events that became reliable predictors of reward. Across probabilistic reinforcement, shifting action-outcome timing, and contingency degradation, dMSN activity and ACh dynamics remained closely aligned, indicating that dMSNs drive this ACh signal. Consistent with this model, ex vivo and in vivo optogenetic experiments showed that dMSN activity was both sufficient and necessary to generate the ACh pause-rebound, and disrupting this dynamic slowed instrumental learning. We then tested how the ACh pause-rebound shapes DA signaling. Enhancing the ACh rebound during fixed-ratio 1 learning increased reward-evoked DA release, but the same manipulation had no detectable effect without reward, indicating that ACh facilitates DA release only when dopaminergic input is engaged. Supporting this state-dependent gating model, optogenetic stimulation of nigrostriatal DA terminals produced a larger DA response when delivered during the ACh rebound than during the ACh dip. Increasing response effort across fixed-ratio schedules deepened the ACh dip and enhanced reward-evoked DA release, whereas the rebound remained relatively stable. Together, these findings identify a dMSN-driven ACh pause-rebound mechanism that encodes reward-predictive salience and gates reward-related DA signaling to promote acquisition of action-outcome associations.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Mu Opioid Receptors on Nucleus Accumbens Cholinergic Interneurons Regulate Dopamine Uptake via a Local Circuit Mechanism

Authors: *A. R. BASHFORD, K. R. SAMSON, Z. D. BRODNIK, R. A. ESPAÑA; Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Opioid use disorder remains a major public health challenge, yet the neural mechanisms by which opioids alter dopamine signaling are not fully understood. Opioids are classically thought to increase dopamine transmission via mu opioid receptor (MOR)-mediated

disinhibition of ventral tegmental area dopamine neurons. However, our laboratory has shown that the MOR agonist oxycodone reduces dopamine uptake in nucleus accumbens (NAc) brain slices lacking intact midbrain circuitry, suggesting a local mechanism of action. Using ex vivo fast-scan cyclic voltammetry (FSCV), we recently found that multiple MOR agonists reduce dopamine uptake in the NAc, along with preliminary evidence suggesting that cholinergic signaling may underlie this effect. Here, we tested the hypothesis that MORs on NAc cholinergic interneurons mediate opioid-induced reductions in dopamine uptake. To selectively target cholinergic interneuron MORs, we infused a Cre-dependent MOR shRNA adeno-associated virus (AAV) along with a ChAT-Cre AAV bilaterally into the NAc core of female and male Long Evans rats. We confirmed ChAT-specific expression histologically and MOR knockdown by Western blot, with RNAscope validation ongoing. Ex vivo FSCV performed three to four weeks post-infusion showed that MOR knockdown significantly attenuated oxycodone-induced reductions in dopamine uptake, particularly at higher concentrations. To further assess cholinergic interneuron involvement, we expressed inhibitory GiDREADDs selectively in cholinergic interneurons. Chemogenetic inhibition with clozapine-N-oxide produced a concentration-dependent reduction in dopamine uptake, mimicking the effects of oxycodone. Together, these findings suggest that MORs on cholinergic interneurons in the NAc core may be an important part of the local circuit through which opioids regulate dopamine uptake.

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Poster

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Support: This study was supported by grants from the Ministry of Science and Technology of Taiwan (MOST 107-2314-B-002-073 and MOST 108-2410-H-002-110-MY2) and the National Science and Technology Council, Taiwan (NSTC 113-2314-B-002-273-MY3) awarded to M.T.T.

Title: Dopaminergic modulation attenuates reward-learning interference driven by punishment-related exploration

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Abstract: Dopaminergic signaling plays a critical role in reinforcement learning, yet how dopamine modulates the relationship between exploratory behavior and learning interference remains unclear. In real-life decision-making, the same action may lead to reward or punishment

depending on the context, requiring individuals to flexibly balance exploration and exploitation. This study examined whether dopaminergic modulation influences punishment-related exploration and its impact on reward-learning interference. Using a double-blind, between-subject design, participants received placebo (N = 30), the D2/3 receptor antagonist amisulpride (N = 31), or the dopamine precursor L-DOPA (N = 12) and performed a monetary gain- and loss-related instrumental learning task combined with computational modeling. Behavioral results showed that, compared with placebo, both amisulpride and L-DOPA reduced reward-learning interference when reward-learning choices involved punishment. Computational modeling further revealed that, in the amisulpride group, this reduction was associated with decreased exploration in reward-learning trials involving punishment, suggesting that D2/3 receptor-related signaling modulates the link between exploration and interference. In contrast, L-DOPA did not further enhance exploration in trials involving punishment, indicating that increased dopamine synthesis may not exert a simple linear effect on learning interference. Together, these findings suggest that dopaminergic modulation shapes the relationship between punishment-driven exploration and reward-learning interference, providing insight into dopamine-dependent mechanisms underlying adaptive and maladaptive learning.

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Poster

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Program #/Poster #: PSTR280.08/HH14

Topic: I.03. Decision Making

Title: Dopamine influences risk preference through value learning, not the utility function

Authors: *C. SUN, C. BAO, J. C. ERLICH;
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Abstract: Dopamine (DA) has been linked to risk preference in laboratory and clinical settings. However, risk preference is not a unitary process: a bias toward risky options can arise from a stable utility function that transforms known offers into choice, or from learning that shapes the evaluation of uncertain offers. Whether DA acts through utility, learning, or both has been unresolved because most paradigms confound these processes. We dissociated learning from utility using two risky-choice tasks for freely moving mice that shared the same trial structure but differed in outcome uncertainty. Mice chose between a guaranteed surebet and a probabilistic lottery on a trial-by-trial basis. In the cued task, a sound signaled the current lottery offer, so expert choice required little ongoing learning. In the uncued task, the sound was uninformative and lottery offers changed in blocks, requiring continuous outcome learning. Logistic regression confirmed this dissociation: uncued choices showed strong sensitivity to the previous outcome, whereas this effect was near-absent in the cued task. Systemic administration of pramipexole (PPX), a D2/3 receptor agonist, increased risk-seeking only in the uncued task, shifting the

indifference point through reduced lose-switch; in the cued task, it increased choice noise without changing risk preference. Strikingly, fiber photometry recordings of nucleus accumbens DA release revealed canonical reward prediction error (RPE) signals at outcome in both tasks, with similar magnitude. Thus, minimal learning in the cued task cannot be explained by absent or weaker DA RPEs; instead, an intact teaching signal is behaviorally disconnected when learning is not required. To quantify this disconnection, we fit a mixture-of-agents model combining a non-learning utility agent, a model-free TD-learning agent, and perseveration. Cued choice was dominated by the utility agent, with negligible contribution from the learning agent, meaning that the value updated by DA RPEs scarcely controlled choice. PPX reduced learning rate and choice precision while sparing the utility function and mixture weights; because the learning agent controlled choice mainly in the uncued task, reduced learning selectively shifted risk preference there. Together, these results indicate that DA is not a general risk-preference signal. Instead, DA influences risk preference through value learning, with behavioral consequences gated by whether learned values control choice. This framework helps reconcile contradictions in the risk literature, including why dopaminergic therapy promotes gambling-like behavior only in specific behavioral contexts.

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Poster

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Topic: I.10. Human Learning and Cognition

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Title: Model-based inference of specific rewards in the lateral orbitofrontal cortex

Authors: *Q. LIU[1], Y. ZHAO[2], T. KHAN[3], N. MOUSSA[1], G. SCHOENBAUM[1], T. KAHNT[1]; [1]Natl. Inst. of Drug Abuse, Baltimore, MD; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]Northwestern Univ., Chicago, IL

Abstract: Model-based behavior requires mental simulation of outcomes that have never been directly experienced. Sensory preconditioning (SPC) provides a framework for studying such inference: after neutral cue pairs are learned (A → B, C → D), one cue from each pair is directly conditioned (B → reward, D → no reward), and responses to all cues are tested under extinction. Responding to preconditioned cue A over C indicates inference of the reward associated with B. Prior work suggests that orbitofrontal cortex (OFC) is necessary for responding to preconditioned (but not directly conditioned) cues during the probe phase. However, it remains unclear whether behavioral responses to preconditioned cues reflect inference of specific outcomes or cached scalar value, and how OFC subregions represent inferred compared to

directly learned cue-outcome associations. We tested this question using a modified SPC task with two food odor rewards and outcome-specific devaluation. Participants (N=32; 21F/11M; ages 21-42) consumed a meal matched to one savory or sweet food odor, allowing us to test whether devaluation reduces responding to both directly conditioned and preconditioned cues associated with that outcome. After the meal, participants showed reduced liking of the sated odor and decreased choices of directly conditioned cues paired with that odor. Critically, choices were also reduced for preconditioned cues predictive of the devalued reward, indicating that subjects inferred specific outcomes associated with cues rather than their learned values. Functional MRI data was analyzed using representational similarity analysis (RSA). During the pre-meal probe phase, directly conditioned and preconditioned cues evoked dissociable representations of reward identity in the OFC, suggesting that inferred and directly learned cue-outcome associations are represented in distinct OFC subregions. Moreover, activity patterns in right lateral OFC distinguished between conditioned and preconditioned cues, and this effect was stronger in the pre- compared to the post-meal phase of the task. In contrast, vmPFC/medial OFC tracked subjective value (liking ratings) of predicted outcomes across both conditioned and preconditioned cues and phases (pre- vs post-meal). Together, these findings suggest that people make inferences about specific outcomes rather than cached scalar value, which are encoded in the OFC. Importantly, OFC is specifically recruited during inference and especially when these inferences are performed for the first time. In contrast, activity in vmPFC/medial OFC tracks subjective value across both experienced and inferred cue-outcome relationships.

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Poster

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Topic: I.10. Human Learning and Cognition

Support: NSF GRFP Fellow (ES)
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Title: The Role of the Orbitofrontal Cortex, Anterior Cingulate Cortex, and Hippocampus in Adaptive Precision of Interval Timing using Human Single Unit and Local Field Potential Recordings

Authors: *E. E. SANDOVAL[1], N. ACHARA[2], D. R. QUIROGA-MARTINEZ[5], C. HOY[6], K. D. LAXER[7], J. J. LIN[8], M. R. DEWEESE[3], J. ZHENG[9], R. T. KNIGHT[4];
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CPMC, San Francisco, CA; [8]Dept. of Neurol., [9]Neurolog. Surgery and Biomed. Engin., Univ. of California, Davis, Sacramento, CA

Abstract: Reward prediction errors (RPE) are critical for goal-driven behavior and can be used to monitor performance on different tasks. In a previously designed and tested interval timing task with adaptive feedback using intracranial recordings in epileptic patients, we found that patients with intractable epilepsy rely on positive RPE (pRPEs) to flexibly modify behavior according to task demands. Similarly, it was found that mesoscopic high frequency activity (HFA, 70-150 Hz) was biased towards reflecting pRPEs over negative RPEs (nRPEs) in both dorsomedial prefrontal cortex (DMPFC) and insula. It remains unclear what other regions such as orbitofrontal cortex and hippocampus are doing during this task, and whether the effects seen in mesoscopic activity in DMPFC agree with effects on the single neuron level. Using Behnke-Fried electrodes in a subset of these patients (n=12), we collected microwire local field potential (LFP) data and extracted single unit activities from anterior cingulate cortex (ACC), hippocampus (HPC), and orbitofrontal cortex (HPC). We found that 38% of OFC units encoded pRPEs at feedback, with only 6% encoding nRPEs. 50% of ACC units encoded reward at feedback, with 28% encoding RPEs. Finally, we found a more varied response in hippocampus with a significant but smaller percentage of units encoding reward, RPEs, precision, and elapsed time during feedback. The LFP of OFC macrocontacts revealed beta activity (15-30 Hz) that distinguished rewards and pRPEs at feedback, while theta activity (4-8 Hz) around trial onset distinguished the history of nRPEs and expected reward, indicating increased cognitive control. Combined with previous behavioral results in our lab that demonstrated pRPEs are used to change behavioral performance over nRPEs, this highlights the role of OFC and ACC in encoding valenced RPEs that are productive for goal-directed behavior.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Program #/Poster #: PSTR280.11/HH17

Topic: I.10. Human Learning and Cognition

Title: Similar Learning, Divergent Recall: Distinct Prediction Error Mechanisms in Test Anxiety

Authors: L. LANDRY[1,2], ***E. A. BOURASSA-PRICE**[3];
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Abstract: The error-related negativity (ERN) is a negative-going deflection on electroencephalography (EEG) following errors, localized to the dorsal anterior cingulate cortex

(dACC). Prior work suggests that anxiety is associated with larger ERN amplitudes, reflecting increased sensitivity to errors. However, we have observed reduced ERN amplitudes in individuals with high test anxiety (HTA) on a go/no-go task, raising the possibility of impaired error monitoring. To test this, participants were classified as HTA or low test anxiety (LTA) using the Performance Evaluation Anxiety Task (PEAT) and completed a time-estimation task during EEG recording. During a learning phase, participants learned to respond 1700 ms (± 100 ms) after a cue under none, veridical, or contrived feedback (50% error, randomized). In a subsequent recall phase, veridical feedback was removed. We hypothesized that HTA would show impaired learning and recall, along with reduced ERN and feedback-related negativity (FRN) amplitudes. Behaviorally, groups performed similarly during learning; however, during recall, LTA performance deteriorated rapidly, whereas HTA maintained performance. ERN and FRN amplitudes did not differ between groups. Trial-level analyses revealed dissociable learning signals across error-related (ERN/FRN), reward-related (feedback-related positivity, FRP), and control-related (theta/beta ratio, TBR) activity. In HTA, larger ERN and FRN amplitudes predicted reduced next-trial deviation (i.e. task improvement), whereas in LTA, improvement was predicted by FRP. In both groups, higher TBR predicted improvement. These findings suggest that HTA and LTA achieve comparable learning through distinct mechanisms, reflecting differential reliance on negative versus positive prediction error signals during performance monitoring. Consistent with this, HTA recall stability is supported by ERN/FRN signals that remain predictive in the absence of feedback, whereas LTA rely on FRP-related signals that diminish when feedback is removed or unreliable. Critically, these results challenge the hypothesis that reduced ERN amplitude in HTA reflects impaired error monitoring, and instead indicate differences in how dACC performance monitoring signals are utilized to allocate control.

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Poster

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Title: Determining the organization of value-based and value-orthogonal prediction error signals during learning

Authors: *P. P. WITKOWSKI, S. YOUNIS, V. ATTANTI, G. SCHOENBAUM, T. KAHNT; Natl. Inst. on Drug Abuse Intramural Res. Program, Baltimore, MD

Abstract: Recent work has shown that the dopaminergic midbrain and ventral striatum signal prediction errors (PE) for reward features beyond scalar value, such as reward identity. However, the organization of these error signals remains unclear. The current experiment tests whether value-based and value-orthogonal PEs are coded in separable signals, and if so, whether the organization of these signals changes in different regions of the brain. We scanned participants (N=17; 4 sessions per participant) while they engaged in a novel learning task in which participants chose between 4 different house stimuli that contained a specific reward (food or water) at a specific amount (low or high). Their goal was to accumulate as many of both resources as possible throughout the task. After each trial a random amount of food and/or water was lost, requiring participants to flexibly determine which reward to pursue in each trial. Further, the type and magnitude of reward available at each house changed over time, requiring participants to actively track both features of the outcome, and evoking identity and magnitude PEs, respectively. We used functional magnetic resonance imaging (fMRI) to measure responses to these PEs in the midbrain and ventral striatum. We show that participants chose the needed resource, and highest-magnitude option of this resource, more often than chance (both $p<0.001$). We then modeled neural responses to outcomes by correlating BOLD signals with identity PEs and magnitude PEs generated from a reinforcement learning model. Activity in ventral midbrain voxels showed significant correlations with both identity PEs and magnitude PEs (both pTFCE <0.05), which had spatially distinct representations ($p=0.003$). This may support learning predictions for outcomes defined by these features. In contrast, the ventral striatum coded distinct signals for water magnitude PEs versus food magnitude PEs ($p=0.008$), but not identity PEs, suggesting that this region codes the motivational value of specific types of outcomes. These results suggest that the format of prediction errors may depend on their computational purpose.

Disclosures: P.P. Witkowski: None. **S. Younis:** None. **V. Attanti:** None. **G. Schoenbaum:** None. **T. Kahnt:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.13/HH19

Topic: I.03. Decision Making

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Title: Basal ganglia pathways oppositely shift neural activity along the decision axis

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Abstract: The cortex and basal ganglia are organized into multiple parallel loops that serve motor, limbic, and cognitive functions. The classic model of cortico-basal ganglia interactions posits that within each loop, the direct pathway of the basal ganglia activates the cortex and the indirect pathway inhibits it. While this model has found support in the motor domain, whether opponent control by the two pathways extends to the cognitive domain remains unknown. Here, we record from anterior cingulate cortex (ACC) and dorsomedial striatum (DMS) while optogenetically inhibiting direct or indirect pathway neurons in DMS, as mice perform an accumulation-of-evidence task in virtual reality. Inconsistent with the classic model, the manipulations do not produce opponent changes in overall ACC activity. Instead, the pathways exert opponent influence over a subpopulation of ACC neurons that encode accumulated sensory evidence, the task-relevant decision variable. The direction of the modulation depends on a neuron's tuning to ipsilateral versus contralateral evidence, such that the two pathways generate opponent shifts in coding specifically along the decision axis. Thus, these results uncover unexpected specificity of the DMS pathways on the cortex, with the two pathways exerting opponent control not on overall activity but on coding of the relevant decision variable. To understand the circuit mechanisms underlying this specificity, we are now testing predictions of two mechanistic circuit models: i) a distributed basal ganglia-cortical circuit for evidence integration, and ii) a cortico-thalamic evidence integrator that is biased by basal ganglia inputs. The models are being tested through deep brain imaging of the two pathways, and recordings paired with pathway-specific inhibition throughout the loop (including substantia nigra pars reticulata, ventromedial thalamus, and superior colliculus). Together, we expect this will give rise to a more accurate model of how the basal ganglia and cortex interact to support cognition.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.14/HH20

Topic: I.10. Human Learning and Cognition

Support: This study was supported by grants from the Ministry of Science and Technology of Taiwan (MOST 107-2314-B-002-073 and MOST 108-2410-H-002-110-MY2) and the National Science and Technology Council, Taiwan (NSTC 113-2314-B-002-273-MY3) awarded to M.T.T.

Title: Punishment history interferes with reward learning under high monetary incentives

Authors: C.-Y. CHOU[1], W.-W. LIN[2], ***M.-T. TSENG**[1];
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Abstract: Monetary incentive magnitude is an important factor in modulating motivation, learning, and decision-making. Although reward and punishment learning have often been studied separately, it remains unclear how incentive magnitude shapes their interaction at the behavioral and neural levels. To address this question, we designed a probabilistic instrumental learning task with two monetary incentive conditions, 1 TWD and 25 TWD. Some options were associated only with reward or punishment learning, whereas others appeared in both contexts, allowing us to examine how punishment history influences reward learning. Thirty healthy participants underwent functional magnetic resonance imaging (fMRI) while performing the task. Behavioral results showed that in the 25 TWD condition (but not in the 1 TWD condition), reward-learning performance declined when reward-learning choices involved punishment history, whereas punishment learning was not clearly affected. Computational modeling showed that reward learning was associated with less exploration than punishment learning when each learning type was examined separately, indicating a more exploitative strategy for reward maximization and a more exploratory strategy for punishment avoidance. fMRI analyses further showed that, under high monetary incentives, increased exploration in reward-learning trials with punishment history was accompanied by enhanced activation in exploration-related prefrontal regions. Together, these findings suggest that higher monetary incentives amplify punishment-related exploration, which may interfere with the exploration-exploitation balance required for effective reward learning.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.15/HH21

Topic: I.03. Decision Making

Title: Neural implementation of temporal difference error via meta reinforcement learning

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Abstract: Dopamine response has been thought to encode the temporal difference error in reinforcement learning. Recent experimental studies captured the key aspects of temporal difference error in the dopamine response, leading to an evidence for a hard-wired circuit computing the temporal difference error in the brain. However, a neural network model for computing the temporal difference error within the framework of reinforcement learning has not been developed yet. Here, we develop such model by learning to produce the temporal difference error and using the approximate error for reinforcement learning. Our model performance was comparable to the standard models. Analysis of trained networks predicts that the correlation between reward and value increases with layer depth. In sum, our work provides a reinforcement learning framework to generate dopamine response in a network, opening the door to develop realistic models to understand dopamine activity.

Disclosures: C. Kim: None. **C.C. Chow:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR280.16/HH22

Topic: I.10. Human Learning and Cognition

Support: ISF Grant 258/20

Title: Neurobiology of placebo-nocebo effects modulated by belief networks of brain

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Abstract: Thoughts and beliefs can exert measurable physiological effects on the body. Placebo and nocebo (pl-nb) interventions provide a useful model for investigating such mechanisms because inert manipulations can produce positive or negative outcomes through contextual and expectancy-driven processes rather than direct physiological action. Moreover, preclinical evidence suggests that neural projections from the anterior insula to posterior insula (PI) modulate conditioned immune responses in rodents, potentially representing a mechanistic substrate for expectancy-driven physiological effects. Here, we tested the hypothesis that verbal pl-nb manipulations and explicit belief states, operationalized through belief judgments, recruit overlapping neural circuitry involving the insular cortex (IC).Male participants (n = 13; age 18-35 years) underwent functional MRI while completing two categories of questions: (1) belief-related questions probing prior beliefs and (2) factual questions involving everyday knowledge. In a separate experimental manipulation, pl-nb states were induced using verbal information and

instructional priming while participants remained in the scanner. Resting-state scans were subsequently acquired following each priming condition.To investigate insular functional dynamics, we adopted an approach based on the tripartite model of the IC, partitioning the IC into dorsal anterior (dAI), ventral anterior (vAI), and PI. Seed-based functional connectivity (FC) analyses identified brain regions exhibiting differential connectivity patterns across pl-nb conditions. Comparisons between nocebo and placebo conditions revealed significant differences in FC involving right vAI and right PI seeds, suggesting differential modulation of insular networks by expectancy state. Regions commonly engaged during belief versus factual judgments were subsequently compared with regions showing differential connectivity during pl-nb manipulation. Convergent effects were observed in bilateral lingual gyrus, right superior parietal lobule, and right angular gyrus, which were both activated during belief processing and differentially connected with parcellated IC regions during expectancy manipulation.Building upon these preliminary findings, we aim to expand the cohort size and include female participants to rigorously characterize the neurobiological mechanisms underlying pl-nb responses. Understanding how cognitive expectancies alter functional brain networks may provide mechanistic insight into how beliefs influence physiological outcomes and inform future therapeutic interventions.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.17/Web Only

Topic: I.10. Human Learning and Cognition

Support: JSPS-KAKENHI 23K27952

Title: Exploring the generalization potential of decoded fMRI-neurofeedback in prospective memory training

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Abstract: [Motivation/problem statement]
Prospective memory (PM), the ability to remember and execute intended actions in the future, plays important roles in daily life. PM is often impaired by aging or brain injury, but no effective method is known for intervention. We explored the potential of fMRI neurofeedback (NF) by modulating frontopolar cortex (FP) activity in healthy adults. We examined whether (1) task-specific NF training can improve behavioral performance for event-based PM (EBPM), a form of

PM triggered by external cues, and (2) this intervention generalizes to another form of PM, or time-based PM (TBPM) triggered by the passage of time.
[Methods]
34 participants underwent a functional localizer run during an EBPM task which consists of detecting deviant visual targets while performing a background word recognition task. After two sessions of NF training (real or sham, 30 min), they again performed the same EBPM task. Before and after NF training, participants also performed a TBPM task which consists of pressing a button every 30 s during the same background task. During NF training, FP activity was decoded by computing Pearson's correlation coefficients between real-time FP activation and activation maps derived from the localizer run. The resulting correlation scores were visualized every 1 s on the screen, which guided participants to regulate FP activity without explicit instruction. Participants in the Sham group received the same training with feedback stimuli unrelated to actual FP activity.
[Results]
For EBPM, behavioral effects of NF on reaction times were examined by treating Intervention (pre vs. post) and Group (NF vs. Sham) as fixed effects. We found a significant Intervention x Group interaction, indicating that the NF group responded faster than the Sham group after intervention. The magnitude of this behavioral improvement correlated with correlation scores during NF only in the NF group. For TBPM, we found a significant Intervention x Group interaction in accuracy costs during the background task, suggesting that the NF training partially improved TBPM performance.
[Conclusion]
Our results show that brief NF training of FP activity can effectively enhance PM performance and may provide an individually customized tool for cognitive rehabilitation.

Disclosures: S. Takeda: None. **K. Takano:** None. **K. Nakamura:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR280.18/HH23

Topic: I.03. Decision Making

Title: Phase Correlations and Consistency are Associated with Information Completeness During Multi-Attribute Decision-Making

Authors: *C. C. LI[1], A. L. SAMPSON[2], E. E. EMERIC[3], W. J. LIPSKI[6], S. MOREIRA GONZALEZ[7], A. DAMIANI[8], J. A. GONZÁLEZ-MARTÍNEZ[6], S. V. SARMA[4], V. STUPHORN[2], E. NIEBUR[5];
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Abstract: Phase relationships between brain regions have been argued to be necessary for coordinating the activity of neurons across spatial scales. We investigate this in the context of a multi-attribute decision-making task performed by epilepsy patients while undergoing stereoelectroencephalography (sEEG) recording. In each trial of the task, patients were presented with two options, each defined by a monetary reward amount and a probability of winning it. Subjects could freely examine the two attributes of each option by unmasking their values one at a time before making a choice. This inspection period required integration of previously viewed values with recently seen values to make a well-reasoned decision, which likely requires coordination across brain regions. As such, we analyzed whether phase consistency and correlations emerged during these periods. We filtered the sEEG recorded at each contact from 5-40 Hz and isolated 0.5s windows aligned to inspection events. At each sampled time point in these windows, we computed the inter-trial phase clustering value (ITPC), the extent to which a phase angle (e.g., peak or trough) consistently occurs in the broadband oscillation across trials at a given time point. We found a sharp increase in ITPC 0.15s following the onset of an inspection event, but only when this was the inspection of the second attribute of an option (not the first). This effect was localized in the medial frontal cortex, suggesting that this area represents whether all information about an option has been accessed. To quantify phase relationships, for two of the medial frontal sEEG probes (which each comprised at least 12 evenly spaced recording electrode contacts) where we found this spike in ITPC, we computed, timepoint-by-timepoint, the circular-linear correlation between the position of the electrodes on the probe and the instantaneous phase angle measured by those electrodes. We found that at and around 0.15s after the onset of inspection events, circular-linear correlation was significantly higher on second-attribute inspections than first-attribute inspections. Together, these findings indicate that phase correlations and consistency may support coordination of activity required for information integration.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Program #/Poster #: PSTR280.19/HH24

Topic: I.03. Decision Making

Support: DAPA Grant No. 915145201

Title: Reward outcome gates prefrontal control of motor cortex during reinforcement learning

Authors: *S. LEE[1], S.-H. KIM[2], M.-K. KIM[3], J.-W. SOHN[4,2], S.-P. KIM[1];
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Abstract: Adaptive choice requires continuously updating the value of available options from reward feedback. While matching behavior in dynamic foraging has been studied extensively, how the dorsolateral prefrontal cortex (DLPFC) and primary motor cortex (M1) interact to support this value updating remains unknown. We recorded M1 and DLPFC neural populations simultaneously in two macaque monkeys (Subject B: 24 sessions; Subject C: 6 sessions) performing a probabilistic two-alternative matching task, in which the reward probabilities of the two options varied block-wise across seven levels, with no explicit cue signaling the transitions. The Choice behavior was well captured by a standard reinforcement learning model. By fitting multi-population recurrent switching linear dynamical systems (rSLDS) jointly to DLPFC and M1 activity, we found that both the chosen value and the reward outcome—the primary drivers for value updating—were robustly encoded in the latent states of each population throughout the trial, persisting into the inter-trial interval (ITI). To probe the directional interaction during this update phase, we computed inter-region control energy—defined as the network control cost of driving one region's ITI state through the cross-region coupling dynamics. The control energy revealed a directional, reward-dependent asymmetry: the reward-dependence (β_{reward}) of prefrontal-to-motor (DLPFC→M1) control energy was significantly more negative than that of the motor-to-prefrontal (M1→DLPFC) direction (Subject B, median $\Delta=-0.28$, $p=9.5\times10^{-7}$; Subject C, median $\Delta=-0.13$, $p=0.031$, Wilcoxon signed-rank test). This indicates that unrewarded trials selectively raised the energy cost of driving M1 state through DLPFC, whereas rewards lowered this cost. Critically, this directional asymmetry was highly specific to the immediate reward outcome and not to the maintained value estimate; the value-dependence of control energy (β_{value}) exhibited minimal or no significant directional dependence (Subject B, median $\Delta=-0.001$, $p=0.495$; Subject C, median $\Delta=0.09$, $p=0.031$, Wilcoxon signed-rank). These results show that the moment-to-moment reward outcome—rather than the maintained value estimate—dynamically gates the controllability of the motor cortex by the prefrontal cortex during reinforcement learning to support value updating in dynamic foraging.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Topic: I.03. Decision Making

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National Natural Science Foundation of China Grants (32071090)
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Title: Neurocomputational Mechanisms of Asymmetric Learning from Outcomes with Different Valences

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Abstract: Human decision-making is characterized by loss aversion, with prospective losses exerting a stronger influence than gains. However, it remains unclear how retrospective and simultaneously experienced gains and losses are represented and integrated in guiding learning and decision-making. Here, we combined behavioral experiments, computational modeling, eye tracking, and electroencephalography (EEG) to investigate multi-outcome learning. Across four experiments with human participants (N = 196), participants performed a reinforcement learning task in which each choice yielded both monetary gain and loss. Behavioral analyses revealed a robust valence asymmetry: individuals systematically overweighted gains relative to losses for future choices. Computational modeling further showed that this asymmetry arose from faster learning from gains than losses. Eye-tracking results demonstrated that participants preferentially attended to gains before losses, and that this attentional latency predicted individual differences in learning asymmetry. Consistent with this temporal prioritization, pupillometry revealed dissociable prediction-error responses, with gain-related signals preceding those related to loss. EEG analyses further identified temporally and spatially dissociable prediction-error (PE) signals, with earlier parietal encoding of gain PEs and later frontal encoding of loss PEs. Moreover, neural sensitivity to loss PEs significantly predicted learning asymmetry. Critically, an independent gambling task revealed no relationship between individual loss aversion and learning asymmetry, indicating a dissociation between prospective valuation and retrospective learning mechanisms. Together, these findings reveal a learning asymmetry dominated by gains when choices yielded outcomes with different valences, a fundamental dissociation between prospective and retrospective processing: whereas prospective decisions are biased toward losses, retrospective learning is biased toward gains, driven by temporally prioritized and spatially dissociable neural processing of competing outcomes.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Program #/Poster #: PSTR280.21/HH26

Topic: I.03. Decision Making

Support: NSF Grant 2237795
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Title: Spatiotemporal Decoding of Explore Exploit Decisions in the Human Brain

Authors: *R. YADAV[1], J. ROMERO[3], J. M. STEPHEN[4], J. M. HOUCK[5], J. F. CAVANAGH[2], V. D. COSTA[6], J. HOGEVEEN[7];
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Abstract: Adaptive behavior requires flexibly shifting between exploiting familiar rewards and exploring novel opportunities. These explore-exploit decisions are implemented via a distributed brain network—anchored in frontopolar cortex (FPC) and ventromedial prefrontal cortex (vmPFC)—that computes the total value of a given choice by weighting the immediate value of familiar options against the latent future value of exploration. Capturing the precise temporal dynamics of these neural computations across spatially distributed cortical networks is critical to resolving how the brain manages this tradeoff. Here, we combined magnetoencephalography (MEG) with partially observable Markov decision process (POMDP) modeling during a reinforcement learning task. By decoding POMDP-derived choice policies in MEG source space, we mapped the precise spatiotemporal emergence of explore-exploit decisions across the cortex. We demonstrate that explore-exploit policy implementation unfolds via a hierarchical functional dissociation across the rostral prefrontal cortex. During decision formation, the lateral FPC initiates the strategic shift toward exploration hundreds of milliseconds before choice execution. Conversely, vmPFC and orbitofrontal cortex (OFC) do not exhibit early significant divergence from the baseline exploitative trace on exploration trials, displaying only a delayed, transient peak prior to choice execution. Following feedback, the vmPFC and OFC transition to a sustained representation of the choice's empirical value to update reward expectancies and guide future actions. Mapping reinforcement learning variables onto millisecond-resolved neural data reveals how the human brain resolves the explore-exploit dilemma: through early strategic initiation of exploration in the FPC, a delayed exploratory shift in vmPFC and OFC, and sustained outcome evaluation to optimize future actions.

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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

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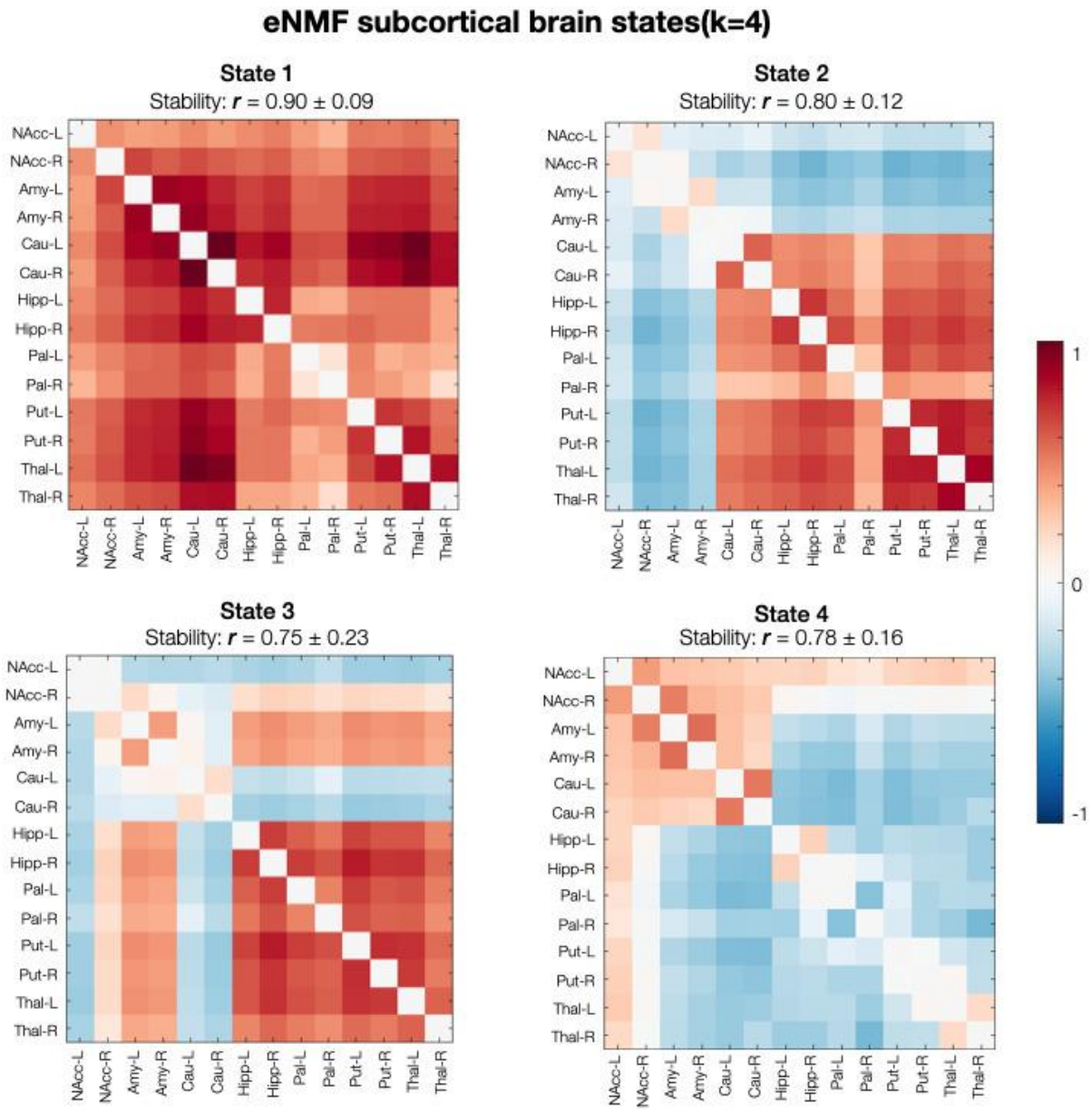
Topic: I.06. Social Cognition

Support: The National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2026-25471465).

Title: Characterizing dynamic subcortical brain states through extended non-negativematrix factorization

Authors: *J. ANN[1], S. JEON[2], S. KIM[1], B. PARK[3];
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Abstract: Dynamic functional connectivity (dFC) captures time-varying interactions among brain regions and has been widely used to identify diverse brain states. The eNMF extends conventional NMF by accommodating both positive and negative connectivity while preserving an interpretable factorization framework. In this study, we applied eNMF to identify dynamic subcortical network states using resting-state fMRI data. We analyzed preprocessed resting-state fMRI data from 1,064 participants, provided by the Human Connectome Project. Regional mean time series were extracted from 14 subcortical regions defined by the FreeSurfer aseg atlas. Then we conducted signal preprocessing including detrending, despiking, and band-pass filtering at 0.008-0.09 Hz. Individual dFC among the 14 regions was estimated with about 30-s sliding window. All resulting dFC vectors were concatenated and decomposed using eNMF. We identified subcortical network states and evaluated the reproducibility using a label permutation approach. The eNMF identified 4 subcortical network states with distinct profiles. State 1, 2, 3, and 4 networks showed highly reproducible and distributed as: state1: broadly positive, overall connections, state2: the basal ganglia-thalamic coupling with weaker or negative limbic coupling, state 3: limbic-striatal coupling, and state 4: negatively segregated pattern (reproducibility: $r > 0.75$, $p < 0.001$). The identified states were generally reproducible across random initializations, supporting the robustness of the decomposition. By accommodating both positive and negative connectivity values, eNMF provides a useful framework for identifying recurrent subcortical dFC patterns.



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Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

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Program #/Poster #: PSTR280.23/HH28

Topic: I.03. Decision Making

Support: NSTC 114-2410-H-006-002

Title: Effects of Real-Time fMRI Neurofeedback on Neural and Behavioral Markers of Compulsive Buyers

Authors: *L. WEI- HSIANG[1], C. TSAI[2], D.-Y. CHEN[4], C.-C. KUNG[3];
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Abstract: Effects of Real-Time fMRI Neurofeedback on Neural and Behavioral Markers of Compulsive Buying Tendencies
Background and Purpose Compulsive buying (CB) has a prevalence of about 5% and, although not yet included in DSM-5, is considered related to addiction and to deficits in impulse control. Our pilot fMRI data showed that, relative to controls, CB individuals exhibited greater caudate responses during a shopping-decision task and greater posterior cingulate cortex (PCC) responses during a craving task, suggesting an over-reactive reward circuit. Real-time functional MRI neurofeedback (rtfMRI-nf) allows participants to volitionally self-regulate activity in a specific brain region, offering a possible causal route to behavioral change rather than the correlational inferences typical of conventional fMRI. Taking the dorsolateral prefrontal cortex (DLPFC) as the training target, the present study examined whether rtfMRI-nf could strengthen DLPFC activity in CB participants, thereby indirectly inhibiting reward-circuit responses and reducing buying impulses.
Methods Participants aged 18–40 with compulsive-buying tendencies were screened using the CBS and RCBS scales. The experiment followed a pre-test–training–post-test design. The pre- and post-tests comprised two fMRI tasks: a craving task and a buy/no-buy decision task. Eleven CB participants completed six rtfMRI-nf training sessions over two to three weeks, with the ROI localized using a neurosynth dlPFC mask. During training, each participant's dlPFC BOLD signal was extracted in real time and rendered as a horizontal-bar visual interface, guiding participants to develop their own strategies to up-regulate the target region; a debriefing followed each session.
Preliminary Results After dlPFC training, the craving-related modulation of PCC activity in the craving task disappeared, the Buy/NotBuy difference in medial prefrontal cortex during the shopping task was reduced, and medial-region responses were attenuated overall—consistent with the hypothesis that enhanced dlPFC activity inhibits the reward circuit. No significant behavioral differences emerged between the pre- and post-test shopping tasks; nonetheless, the descriptive changes in neural response patterns provide preliminary support that rtfMRI-nf exerts a modulatory effect at the neural level.

Disclosures: L. Wei- Hsiang: None. **C. Tsai:** None. **D. Chen:** None. **C. Kung:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.24/HH29

Topic: I.03. Decision Making

Support: NIDA F31DA063320

Title: Neural Differences in Cognitive and Physical Effort-based Decision Making in Tobacco Use Disorder

Authors: *K. P. SPRY[1], M. A. ADDICOTT[2];
[1]Neurosci. Grad. Program, Wake Forest University, Grad. Sch. of Arts and Sci., Winston Salem, NC; [2]Translational Neurosci., Wake Forest Univ. Sch. of Med., Winston Salem, NC

Abstract: An important feature of healthy decision-making is the willingness to exert effort, either physical or cognitive effort, to obtain rewards. Effort-based decision making (EBDM) evaluates reward value (i.e. magnitude and probability) relative to effort costs; as effort costs increase, rewards may be devalued. Physical and cognitive EBDM may rely on distinct mechanisms and individuals may differentially value/engage cognitive vs. physical effort. Tobacco withdrawal may reduce sensitivity to nondrug reward values, impacting EBDM. To examine this, we explored the neural differences in cognitive and physical EBDM in individuals with tobacco use disorder (iTUD; n = 5). Participants completed the cognitive and physical Effort Expenditure for Rewards Task (EEfRT) during fMRI while smoking as usual (satiated) and after overnight abstention (withdrawn). Cognitive EEfRT required mental arithmetic (high effort) or number matching (low effort). Physical EEfRT required 22 (high) or 15 button presses (low). First-level analyses modeled decision (expected value parametric modulator), task (effort level: high vs. low), and feedback (outcome: win vs. loss). Group analyses used a factorial design with nicotine state (satiated vs. abstinent) and task type (cognitive vs. physical). Whole-brain results were thresholded at a voxel-wise uncorrected $p < 0.005$ and a cluster-level uncorrected $p < 0.05$. During decision, expected value in cognitive vs. physical task was more strongly associated with activation in the right superior frontal cortex, left calcarine cortex, and right precuneus. During task, effort level in cognitive vs. physical task was more strongly associated with activation in left frontal motor and cognitive control regions (precentral, inferior, middle, and superior frontal gyri; supplementary motor area), as well as parietal and temporal regions including right middle frontal and left inferior/middle temporal gyri. Physical vs. cognitive task was more strongly associated with greater activation in ventromedial prefrontal cortex, left precentral gyrus, and medial frontal regions. During feedback, outcome in physical vs. cognitive effort was more strongly associated with activation in a posterior parietal-occipital network, including superior parietal/precuneus, occipital cortex, angular and occipito-temporal regions, cuneus, and right superior/middle temporal gyri with insula involvement. Across all analyses, no significant effects of nicotine state were observed. These findings demonstrate a dissociation between cognitive and physical effort in iTUD, highlighting effort as a multidimensional construct in SUDs.

Disclosures: K.P. Spry: None. **M.A. Addicott:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.25/HH30

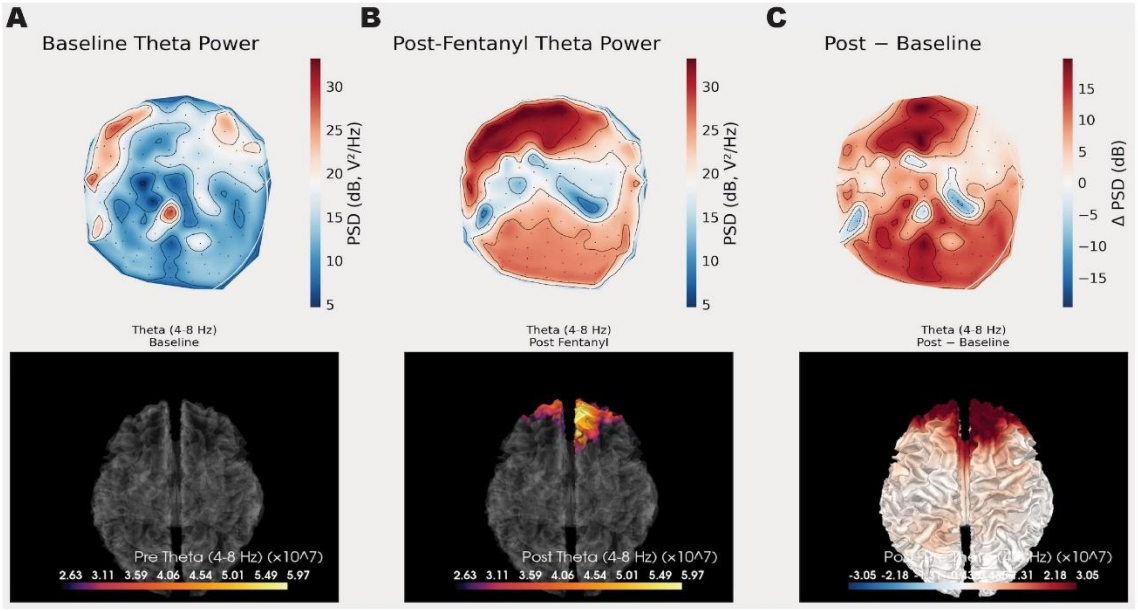
Topic: I.10. Human Learning and Cognition

Support: Characterizing brain dynamic biomarkers of fentanyl using intracranial and high-density electroencephalogram in humans R01DA056593

Title: Oscillator decomposition-based source localization of fentanyl frontal theta: toward circuit-level monitoring of opioid drug effects

Authors: *J. NATARAJ[1], K. NAFTCHI-ARDEBILI[1], R. MATHER[6], S. TOU[2], G. BALANZA[7], A. PANDIT[7], B. MINHAS[8], M. ABATE[3], N. YERRAGUNTLA[4], F. TIAN[9], M. HE[5], P. L. PURDON[7];
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Abstract: Fentanyl produces a frontal theta (4-8 Hz) oscillation, a candidate EEG biomarker of opioid drug effect. Its generators are unestablished, but frontal topography and opioid pharmacology point to underlying circuitry unresolvable by EEG. Source localization is standard for inferring EEG generators, but accuracy is constrained by definitions of signal and noise. Theta is typically isolated by band-pass filtering, which passes all band power, physiological or artifactual. Noise covariance is usually estimated from a single baseline and applied uniformly, failing to capture post-fentanyl changes in noise structure. Here we introduce an anatomically individualized source-localization pipeline that extracts structured theta oscillators using a decomposed oscillator model (dOsc, SOMATA library): a parametric state-space oscillator model giving more robust, physiologically specific estimates than filtering. Each channel is decomposed into a theta oscillator and a broadband residual, serving two purposes: providing a theta estimate and defining condition-specific noise covariances (baseline and post-fentanyl) from residuals, which isolate non-oscillatory noise and maximally avoid spectral leakage. Covariances are truncated at nonzero eigenvalues to address rank deficiency from average referencing and interpolation, which may otherwise inflate near-zero directions into spurious sources. These covariances regularize minimum-norm inverse operators (dSPM), from which source-level theta power is averaged over 4-8 Hz. We recorded high-density EEG from adult surgical patients before and after two fentanyl boluses. In an initial subject, the pipeline recovered a post-fentanyl increase in frontal-medial theta at both sensor and source levels (212s after 2nd fentanyl dose). We show that the pipeline anatomically resolves the fentanyl theta biomarker and localizes its neural generators. This framework offers a robust, generalizable approach for mapping EEG oscillations to neural generators and can inform circuit-level monitoring of opioid drug effects.



Theta-band (4–8 Hz) power at (A) baseline, (B) post-fentanyl, and (C) power difference (post-fentanyl – baseline), shown as scalp topographies (top; anterior view) and cortical source maps (bottom; dorsal view).

Disclosures: J. Nataraj: None. **K. Naftchi-Ardebili:** None. **R. Mather:** None. **S. Tou:** None. **G. Balanza:** None. **A. Pandit:** None. **B. Minhas:** None. **M. Abate:** None. **N. Yerraguntla:** None. **F. Tian:** None. **M. He:** None. **P.L. Purdon:** Other; PLP is a cofounder of PASCALL Systems, a startup company developing closed-loop physiological control for anesthesiology..

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.26/HH31

Topic: I.10. Human Learning and Cognition

Support: NIMH Grant 5R01MH119086-07

Title: The effects of fatigue on feedback-based cue-effort association learning

Authors: *S. HONG[1,3], A. J. CULBRETH[4], V. S. CHIB[2,1,3,5];
[1]Neurosci., [2]Biomed. Engin., Johns Hopkins Sch. of Med., Baltimore, MD; [3]Kennedy Krieger Inst., Baltimore, MD; [4]Psychiatry, Grounds of Spring Grove Hosp. Ctr., Catonsville, MD; [5]Kavli Neurosci. Discovery Institute, Johns Hopkins Univ., Baltimore, MD

Abstract: Learning the appropriate amount of effort required to perform an action is critical for efficient behavior and ultimately choosing whether the benefits of an action are worth its costs. Although effort learning is fundamental to everyday action, it is seldom the focus of reinforcement learning designs. Instead, effort is often studied in paradigms in which effort is

traded for reward using well-learned effort quantities, making it difficult to isolate how people learn and represent effort itself. Furthermore, while physical fatigue is known to reduce willingness to exert effort for reward, the impact of fatigue on how individuals learn about and perceive effort remains poorly understood. To address this question, participants completed a cue-effort association task in which they learned to associate visual cues with specific grip-force levels using a hand dynamometer. Participants received trial-by-trial error feedback indicating how closely their exerted force matched the target force level, but made no choices regarding whether or not to pursue effort demands and received no rewards, allowing effort learning to be examined in isolation. Throughout the experiment, participants provided ratings of momentary fatigue and subjective effort associated with each cue. The task consisted of three learning blocks involving distinct cue sets, interspersed with test trials to assess learning. Participants demonstrated near-ceiling accuracy on test trials, and their exerted force progressively converged toward target force levels through learning, indicating successful acquisition of cue-effort associations. Subjective effort ratings increased with both momentary fatigue and fatigue accumulation over repeated trials. When analyses were restricted to ratings following force exertion trials, subjective effort ratings were independently predicted by both exerted force and fatigue levels. These findings suggest that subjective effort perception depends not only on the physical demands of an action but also on an individual's current fatigue state. Moreover, the dissociation between successful force learning and fatigue-dependent changes in effort perception suggests that learning an action's required effort and perceiving its subjective cost may rely on partially distinct processes. Future work will extend these findings using functional magnetic resonance imaging (fMRI) to identify the neural mechanisms linking fatigue, effort learning, and effort perception.

Disclosures: S. Hong: None. **A.J. Culbreth:** None. **V.S. Chib:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.27/HH32

Topic: I.10. Human Learning and Cognition

Title: The Impact of Perceived Affective Alignment (PAA) on University Students' Academic and Cognitive Performance

Authors: *M. YAMADA[1], S. YOSHIZAWA[2], K. INOUE[3], Y. TAMORI[4], K. MOGI[5];
[1]Temple Univ. Japan Campus, Tokyo, Japan; [2]Physics, Tokai university, Hiratsuka, Japan; [3]Yokohama Natl. Univ., Yokohama City/Kanagawa Prefecture, Japan; [4]Grad. Sch. of Arts & Sci., The Univ. of Tokyo, Meguro-ku, Tokyo, Japan; [5]Sony Computer Sci. Labs., Shinagawa-Ku, Japan

Abstract: Large Language Models (LLMs) such as ChatGPT have become increasingly prevalent in professional, educational, personal and therapeutic settings (Mohammad et al.,

2026). When it comes to education, the increase in accessibility and practicality of AI usage has raised concerns regarding students' cognitive engagement (Kosmyna et al., 2025) and ethics (Huallpa et al., 2023). Human-AI interactions have been shown to lead to the anthropomorphizing of AI agents, provoking emotional responses and forming relationships (Guingrich & Graziano, 2025). While this attachment is not a replacement for human-human interactions, the emotional support LLM agents provide may impact users' attitudes. While this relationship has been investigated, little is known about the emotional effects human-AI interactions have on humans' cognitive performance. Perceived affective alignment (PAA) is characterized by the AI's linguistic and emotional attunement to the user's emotional state (Kang & Huang, 2026). Considering that studies have found a significant positive correlation between social support and student's cognitive engagement, which in turn resulted in higher academic performance (Achdiyah et al., 2023), our study investigates whether high PAA during AI-assisted study sessions have similar effects. University students complete a pre-knowledge assessment before watching a single standardized pre-recorded lesson. They are then randomly assigned to complete an assignment in one of the following ways: (a) using assistance from an emotionally empathic ("human-like") LLM, (b) an emotionally neutral LLM, or (c) a control group without AI. LLM agents are prompted to be contextually consistent while only changing the emotional tone output, allowing students' performance difference to be attributed to the LLM's emotional tone. Cognitive engagement during the task is assessed with the Cognitive Engagement Scale-Extended (CES-E) (Charsha, 2013) and learning with a post-assignment knowledge test. Student's subjective PAA is measured after the assignment using the Perceived Empathy of Technology Scale (PETS) (Schmidmaier et al., 2024). Participants' cognitive performance is analyzed using ANCOVA with prior knowledge as a covariate. The results determine whether PAA, the perceived emotional attunement in student-AI interaction, significantly affects students' cognitive and academic performance during and after task completion.

Disclosures: M. Yamada: None. **S. Yoshizawa:** None. **K. Inoue:** None. **Y. Tamori:** None. **K. Mogi:** None.

Poster

PSTR280: Neural Mechanisms of Reinforcement Learning and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR280.28/Web Only

Topic: I.10. Human Learning and Cognition

Title: Psychophysiological state of amateur drone-racing athletes and UAV operators

Authors: *S. FEDORCHUK, V. KARAS, O. SHYNKARUK;
Natl. Univ. of Ukraine on Physical Educ. and Sport, Kyiv, Ukraine

Abstract: The beginning of the full-scale invasion in Ukraine has led to a critical need to intensify the training of highly qualified operators of unmanned aerial vehicles (UAVs) in the

shortest possible time. Since drone control requires a person to have extreme concentration, instant reaction, and stress resistance, there is a need for a detailed study of individual neurodynamic and functional properties of the central nervous system. The purpose of the study was to compare the state of psychophysiological functions of amateur drone-racing athletes and active UAV operators. Methods: psychophysiological tests and methods of non-parametric mathematical statistics. The diagnostic complex "Diagnost-1" (M. V. Makarenko, V. S. Lyzogub) was used to determine the state of psychophysiological functions and individual characteristics of the sensorimotor reaction of UAV operators and amateur drone racers. This device measured the indicators of simple visual-motor reaction (SVMRT), one-of-three and two-of-three choice reactions, indicators of the reaction to a moving object (RMO), and indicators of the speed, quality, and quantity of information processing in the "feedback" mode, which determine the functional mobility of nervous processes (FMNP) and the strength of the nervous system. Indicators of dynamic muscular endurance were also evaluated separately for the right and left hands. The study involved 12 amateur drone-racing athletes aged 18-32 and six UAV operators aged 20-38. The results of previous studies revealed certain relationships between the success of flights on FPV simulators and the psychophysiological indicators of amateur athletes. UAV operators were found to have a shorter time of the motor component of the SVMRT in the optimal testing mode ($p < 0,05$) and a shorter time to reach the minimum exposure in the feedback mode ($p < 0,05$). Amateur athletes demonstrated higher FMNP compared to UAV operators ($p < 0,05$): the subjects of this group needed less time to process 120 signals in the feedback mode. In addition, amateur athletes demonstrated a shorter average time in the reaction of anticipation according to the RMO indicators ($p < 0,05$). The obtained empirical data have direct applied value for military and civil aviation. The results of the study can be used for further research, training beginners and amateurs in drone sports, and the popularization of this sport.

Disclosures: S. Fedorchuk: None. **V. Karas:** None. **O. Shynkaruk:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.01/II1

Topic: H.03. Motivation

Support: NIH R01-MH133608 – S01

Title: Topographically Organized Pallidohabenular (EP^{LHb}) Neurons shape learning under threat/reward conflict

Authors: *D. REINA-GUERRA[1], E. KRAFT[2], M. WALLACE[2];
[2]Anat. & Neurobio., [1]Boston Univ., Boston, MA

Abstract: Mice foraging in natural environments must learn to suppress escape from potentially threatening but ultimately harmless stimuli to ensure maximum reward acquisition. Somatostatin-positive neurons of the Entopeduncular Nucleus (EP) project exclusively to the Lateral Habenula (LHb), co-release GABA and Glutamate, and have been shown to signal the rewarding or aversive outcome of actions to guide future behavior. We have shown that silencing synaptic release from these EP^{LHb} neurons increases escape suppression when rewards are present. Here we use intersectional neuroanatomical tract tracing and three-dimensional registration to show that EP^{LHb} neurons are organized topographically by input from either the threat-related Tail of the Striatum (TS) or the reward-related Caudal Ventral Striatum (CVS). We use fiber photometry to show that these topographically organized EP groups differentially signal threat and reward. Finally, we use CRISPR mediated knockdown of either VGAT or VGLUT in EP^{LHb} neurons to show that perturbing the GABA/Glutamate co-release ratio of EP^{LHb} neurons modifies LHb reward signaling and escape suppression behavior.

Disclosures: D. Reina-Guerra: None. **E. Kraft:** None. **M. Wallace:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.02/II2

Topic: H.03. Motivation

Support: NIMH P50 MH 096889
Bren Foundation
Noel Drury Depression Research Institute, UCI Seed Award

Title: Probing in human and mouse the conserved mechanisms for encoding early life adversity in the paraventricular nucleus of the thalamus

Authors: *M. R. TETZLAFF[1], A. FLORIOU-SERVOU[2], M. HARDY[4], C. KOOIKER[3], G. TURECKI[6], T. BARAM[5];
[1]Univ. of California, Irvine, Irvine, CA; [2]Dept. of Anat. & Neurobio., [3]Anat. and Neurobio., UC Irvine, Irvine, CA; [5]Anatomy/Neurobiology; Pediatrics, [4]Univ. of California Irvine, Irvine, CA; [6]McGill Univ., Montréal, QC, Canada

Abstract: Rationale: The paraventricular nucleus of the thalamus (PVT) is an essential integrator of internal states and event salience, adjudicating motivated behaviors. Motivated behaviors are dysregulated by early life adversity (ELA) through incompletely understood mechanisms. We found that neuronal activation in mouse PVT uniquely distinguishes ELA from typical rearing, and that adult modulation of these early-life activated PVT cells restores normative motivated behavior in ELA mice. However, the cell type of activated PVT neurons and the ELA-induced transcriptional changes to these cells remain unknown.This is an important question, because regulation of motivated behaviors is altered also humans with an ELA history, increasing risk for

mental illness. Surprisingly, while neuroimaging suggests similar connectivity networks of human and rodent PVT, there is limited knowledge of the molecular and anatomical characteristics of the human PVT. This work probes the translational potential of molecular features in the PVT by defining shared anatomical and transcriptional features in adult PVT across species.
Methods and Results: This study utilizes TRAP2 mice to selectively assess adult PVT cells which were active during ELA in the first week of life, and MERscope spatial transcriptomics to identify these target cells by expression of select transgenes. We further employ MERscope spatial transcriptomics to characterize the anterior and posterior PVT across several human individuals, and present finalized cross-species comparisons of cellular composition, marker gene expression, and anatomical organization between the mouse and human PVT. We find several genes are shared across species, including those which define cell type in the mouse (ie; DRD2). We find also that, distinct from the mouse, the human PVT is not distinguished by mouse PVT markers NTRK1 or CRHBP, and interestingly, the human PVT but not the mouse PVT contains an interneuron population.
Conclusions: The PVT contains several conserved characteristics across species, which may relate to analogous functions in health and disease. The PVT also contains some genes which are not shared across species, which may narrow target cells or functions for mechanistic and therapeutic approaches. We further evaluate the PVT as a node for encoding early life events by describing adult cell type populations in mice with and without a history of ELA.

Disclosures: M.R. Tetzlaff: None. **A. Floriou-Servou:** None. **M. Hardy:** None. **C. Kooiker:** None. **G. Turecki:** None. **T. Baram:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.03/II3

Topic: H.03. Motivation

Support: George E. Hewitt Foundation for Biomedical Research (Postdoctoral Fellowship)
Swiss National Science Foundation (Postdoc.Mobility fellowship 217810)
National Institutes of Health (MH096889)

Title: Peptide signaling in the paraventricular thalamus is essential for disrupted adult reward behaviors consequent to early-life adversity

Authors: *A. FLORIOU-SERVOU[1], R. WEBER[1], Y. CHEN[2], M. TETZLAFF[1], C. KOOIKER[3], M. T. BIRNIE[2], A. K. SHORT[2], R. ROBERTS[4], H. LIANG[1], M. GANTUZ[1], M. HARDY[1], A. MORTAZAVI[1], T. BARAM[5];
[2]Pediatrics, [3]Anat. and Neurobio., [4]Exptl. Pathology, [5]Anatomy/Neurobiology; Pediatrics, [1]UC Irvine, Irvine, CA

Abstract: Background: Early-life adversity (ELA) is associated with mental health problems later in life, however, the mechanisms by which transient neonatal experiences generate enduring, sex-specific alterations in brain function remain unresolved. The paraventricular thalamus (PVT) is selectively activated during ELA and contributes to dysfunctional reward behavior in adulthood, so we hypothesized that enduring disruptions in adult reward behavior are connected to gene expression changes in the PVT. We first screened actively translated genes of PVT cells activated early in life both at rest and in the context of reward. We found that reward elicited distinct translation programs in ELA versus control (CTL) mice of both sexes. One of the genes strongly regulated by reward and influenced by rearing and sex was the corticotropin-releasing hormone receptor type 1 (*Crhr1*), that senses CRH, a stress-related peptide. Importantly, CRHR1 is expressed in a higher proportion of activated cells in the PVT of ELA mice compared to CTL, so it could mediate the effects of ELA on reward behavior. Therefore, we used CRISPR/Cas9 to delete *Crhr1* specifically in PVT cells activated during the ELA period and we assessed reward behaviors. **Methods**: To isolate and sequence translated genes of early life (P6-P8)-activated PVT cells we crossed Fos-Cre^{ERT2} mice with mice expressing the ribosomal tag EGFP-L10a in a Cre-dependent way. To delete *Crhr1* specifically from early life activated PVT cells, we crossed the Fos-Cre^{ERT2} mice with LSL-FLP mice and delivered a FLP-dependent AAV that expressed Cas9 and RNA guides for *Crhr1* in adult mice. Mice from different groups were randomized during tissue collection and processing, and the experimenters were blinded throughout the experiment. **Results**: Exposure to reward elicited strikingly divergent gene translation programs in ELA versus CTL mice of both sexes, revealing a latent transcriptional state unmasked by reward exposure. CRISPR-Cas9-mediated deletion of *Crhr1* exclusively in ELA-activated PVT neurons normalized reward behaviors in both male and female adult ELA mice. **Conclusions**: Our results 1) indicate that ELA primes the PVT, influencing the way that the PVT responds to reward, 2) highlight PVT's sexually dimorphic nature and 3) point to a critical role of the CRH system in the dysregulation of reward behavior by ELA.

Disclosures: A. Floriou-Servou: None. **R. Weber:** None. **Y. Chen:** None. **M. Tetzlaff:** None. **C. Kooiker:** None. **M.T. Birnie:** None. **A.K. Short:** None. **R. Roberts:** None. **H. Liang:** None. **M. Gantuz:** None. **M. Hardy:** None. **A. Mortazavi:** None. **T. Baram:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.04/II4

Topic: H.03. Motivation

Support: T32 MH112507
BWF CASI 1019469

Title: Lateral Habenula Activity Modulates Adaptive Behavioral State Switching Following Aversive Events

Authors: *J. CHANDRA[1], E. LEWIS[2], N. MEJIA[5], J. MUIR[3], C. MOLINA[3], C. K. KIM[2,4];
[1]Princeton Univ. / UC Davis, Princeton, NJ; [2]Princeton Neurosci. Inst., [4]Omenn-Darling Bioengineering Inst., [3]Princeton Univ., Princeton, NJ; [5]Univ. of California, Davis, Davis, CA

Abstract: The regulation of reward-seeking, such as in the face of conflict or punishment, is an important behavior for animal survival. To investigate the neural basis of reward-seeking under conflict, we presented mice with unexpected foot shocks during reward acquisition, inducing a trade-off between avoidance (freezing) and approach. We hypothesized that the lateral habenula (LHb), a hub interfacing with dopaminergic and serotonergic systems, dynamically shifts between behavioral states and influences resumption of reward-seeking after aversive stimuli. Mice transiently suppressed reward-seeking for ~5 minutes post-shock (n=5), with freezing bouts inversely correlated to licking. Mice without reward cues (n=4) froze significantly longer (P=0.0024; Student's t-test), indicating that reward context buffers aversive responses. Fiber photometry (FP) of LHb neurons using AAV5-Syn-GCaMP6f revealed post-shock LHb suppression that correlated with slower return to licking (n=16), and a generalized linear model (GLM) decoded behavioral state from LHb activity above chance. Optogenetic inhibition of LHb (AAV5-CaMKIIa-ArchT-GFP) delayed reward-seeking across days, reducing it relative to controls (inhibition n=7, control n=12; P=0.0231) and relative to each animal's own baseline (P=0.0025), supporting a causal role (repeated measures 2-way ANOVA with significant interaction, followed by Tukey's multiple comparisons post-hoc test). In addition, ongoing experiments are exploring how LHb activity predicts other types of behavioral state transitions, such as active vs. passive, during the tail suspension test (TST). Together, these findings highlight the LHb as a key modulator of adaptive behavioral switching following aversive events, offering potential insight into neural mechanisms underlying motivational impairments, such as those seen in major depressive disorder and other neuropsychiatric disorders.

Disclosures: J. Chandra: None. **E. lewis:** None. **N. Mejia:** None. **J. Muir:** None. **C. Molina:** None. **C.K. Kim:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.05/II5

Topic: H.03. Motivation

Title: Effects of early onset puberty and peripubertal stress on activity and related behaviors of the mesolimbic dopamine system in female mice

Authors: *H. J. F. MUNSON[1,2,3], Y. ALONSO CARABALLO[1,2,3], P. G. MERMELSTEIN[1,2,3], J. C. LEMOS[1,2,3];
[2]Med. Discovery Team on Addiction, [3]Dept. of Neurosci., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: In recent decades, girls are entering puberty at a much earlier age than ever before, with the average age of pubertal onset decreasing from 13-14 years to 10-11 years. Early onset puberty (EOP) can increase the risk of neuropsychiatric disorders, including substance use disorders (SUDs). Stress during sensitive periods, such as adolescence, can also alter brain development and further increase risk of psychiatric disorders. To assess the interplay between EOP and peripubertal stress, we used a high-fat diet (HFD) model and forced swim stress (FSS) paradigm. After weaning, female mice were pair-housed and assigned to control 10% fat diet or 45% HFD groups. Mice were monitored daily for vaginal opening (VO), and once present, vaginal lavages were performed to determine estrous stage. Mice within each diet group were assigned to either the non-stressed or FSS condition at 4 weeks of age. At 6-7 weeks of age, mice underwent dyadic social interaction and novelty exploration assays followed by sacrifice. Reproductive organ weights were measured and brain tissue was collected. Micro-dissection of the nucleus accumbens (NAc) was sent for high performance liquid chromatography; the ventral tegmental area (VTA) was preserved for RNAscope. HFD animals showed vaginal opening (VO) and reached first estrus significantly earlier than control littermates. While HFD increased overall body mass, there was no difference in ovary weight in respect to body mass or overall gross locomotion. HFD animals showed a trend of increased dopamine synthesis and turnover in the NAc; a significant main effect of HFD on dopamine is present when mice are separated by estrous stage. Additionally, preliminary data suggest increased immediate early gene activation of dopaminergic neurons in the VTA of mice in the HFD group in response to novelty. This elevated level and activity of dopamine as a result of HFD and EOP may drive differences in novelty- and social-related behaviors. HFD animals displayed fewer numbers of rears and shorter cumulative rearing duration compared to the 10% group. Frequency in entering the novel object target zone showed a diet x stress interaction, with 10% FSS animals entering the target zone significantly more than their non-stressed counterparts. Social interaction data suggest that 45% diet animals approached and spent more time affiliated with a same sex conspecific. These data support previous work using HFD to successfully induce EOP and draws a bridge between EOP and subsequent dopaminergic dysregulation. Future work will look to examine impulsivity and maladaptive reward processing in efforts to better understand the mechanistic relationship between EOP and SUDs.

Disclosures: H.J.F. Munson: None. **Y. Alonso Caraballo:** None. **P.G. Mermelstein:** None. **J.C. Lemos:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.06/II6

Topic: H.03. Motivation

Support: RO1 MH132680
F30 MH126615
T32 DA050558

T32 GM008620
T32 DA50558
T32 NS121727
P50 MH096889
The Bren Foundation

Title: Paraventricular Thalamic Neurons Recruited by Early-Life Adversity Mediate Disrupted Adult Reward Behaviors in a Sex-Dependent Manner

Authors: *M. HARDY[1], C. L. KOOIKER[3], M. T. BIRNIE[5], A. FLORIOU-SERVOU[4], Y. CHEN[6], T. Z. BARAM[2];
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Abstract: Background Early-life adversity (ELA) is linked to dysregulated reward behavior and greater vulnerability for psychiatric disorders, including major depressive disorder and substance use disorders, through neurobiological mechanisms that remain largely unknown. In a mouse model of ELA developed by our lab (limited bedding and nesting), we identified persistent, sex-specific disruptions to reward behavior. Specifically, males display suppressed hedonic consumption and females exhibit heightened consumption and motivation for reward. To identify the neurons mediating these effects, we permanently tagged (TRAPed) neurons active during early life using TRAP2 (Fos-iCre) mice. This revealed robust, selective recruitment of the paraventricular thalamus (PVT) during ELA. Here, we use chemogenetic manipulation and calcium imaging with fiber photometry to probe the functional contribution of these PVT TRAP neurons to adult reward behavior disruptions. **Methods** For chemogenetic experiments, TRAP2 (Fos-iCre) mice were crossed with either Cre-dependent inhibitory (Gi) or excitatory (Gq) DREADD mice and a guide cannula was implanted into the anterior or posterior PVT to deliver the DREADD ligand clozapine-N-oxide (CNO) or vehicle. For fiber photometry experiments, TRAP2 mice were crossed with a Cre-dependent FlpO mouse to convert transient Fos activity into permanent FlpO expression. In adulthood, we injected Flp-dependent GCaMP6f (AAV8-EF1α-C_{off}/F_{on}-GCaMP6f) into the anterior or posterior PVT and implanted a fiber optic cannula above the injection site. Calcium activity of anterior and posterior PVT TRAP neurons was recorded across reward-seeking, cue presentation, and consumption in ELA and control mice of both sexes. **Results** Chemogenetic manipulation of early-life-TRAPed neurons in adulthood confirmed their role in disrupted reward behavior: anterior PVT TRAP neurons drive anhedonia-like behavior in ELA males, while posterior PVT TRAP neurons mediate heightened reward consumption in ELA females. Studies using fiber photometry and a home-cage operant device (FED3) to probe the *in vivo* calcium activity dynamics of anterior and posterior PVT TRAP neurons in ELA and control mice during reward behavior are ongoing. **Conclusions** These findings establish the PVT as a major hub of early-life plasticity and identify anterior and posterior PVT as distinct, sex-dependent mediators of aberrant reward behavior following ELA. Ongoing photometry analyses will resolve the *in vivo* activity of early-life-recruited PVT neurons during reward behavior and reveal how ELA persistently alters this activity to drive aberrant reward behavior.

Disclosures: M. Hardy: None. **C.L. Kooiker:** None. **M.T. Birnie:** None. **A. Floriou-Servou:** None. **Y. Chen:** None. **T.Z. Baram:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.07/II7

Topic: H.03. Motivation

Support: Rhode Island INBRE, NIH GM103430-Early Career Development subaward
Rhode Island Foundation 16409_139170
Providence College Provost's Faculty Fellowship

Title: Medial prefrontal cortex ensembles bias action selection during motivational conflict

Authors: K. MCCAFFREY, M. ROHR, F. SCHAUB, A. ASHLEY, C. ARCAND, C. THEODOROU, J. DEVIA, L. BOTELHO, *R. J. POST;
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Abstract: While neural circuits driving single, specific survival behaviors (e.g., food-seeking in states of hunger) are highly conserved and well-characterized, behavior in dynamic environments requires the integration and weighting of information related to multiple, concurrent needs. Though this behavioral plasticity is essential for survival, the mechanisms by which it is implemented are not fully understood. The medial prefrontal cortex (mPFC) shapes action selection, and our previous work demonstrates that two competing stimuli—environmental threat and food—are represented by activity in largely separable mPFC ensembles in hungry mice. Though activity in these neuronal ensembles correlates with behaviors directed toward these different motivations, it remains unclear whether this activity is sufficient for behavioral selection. To determine if activity in mPFC ensembles biases the animal's behavior in response to one competing need over the other, we employed a targeted recombinase in active populations (TRAP) approach to chemogenetically activate and inhibit ensembles responding to either predator odor or food while hunger and environmental threat were in conflict. Male and female TRAP2-Cre mice were injected with a Cre-dependent hM3D(Gq)- or hM4D(Gi)-mCherry AAV in the mPFC. Three weeks later, hM3D/hM4D expression was driven in either threat or food-responsive ensembles, or following exposure to a neutral stimulus as a control. Specifically, mice were injected wither 4-hydroxytamoxifen prior to exposure to the predator odor trimethylthiazoline (TMT), following overnight food deprivation and prior to refeeding, or prior to an odorless control (n = 13-15 mice per group). After allowing three weeks for hM3D/hM4D expression, mice were food-deprived for four hours and injected with CNO or vehicle in counterbalanced trials prior to a behavioral assay in which food was only available adjacent to TMT. Activating predator odor-responsive mPFC ensembles significantly decreased food consumption and time in the odor zone relative to vehicle trials. Similarly, activating food-responsive ensembles increased food-directed behaviors. Inhibiting these ensembles inversely

affected behavior, and activating neutral ensembles had no behavioral effect. In the absence of predator odor, mPFC ensemble activity had no effect on food consumption. While experiments manipulating ensembles elsewhere in the cortex to determine the specificity of this function to the mPFC are ongoing, our results thus far suggest that activity in independent mPFC ensembles representing competing motivations may prioritize behavior toward one need at the expense of another.

Disclosures: K. McCaffrey: None. **M. Rohr:** None. **F. Schaub:** None. **A. Ashley:** None. **C. Arcand:** None. **C. Theodorou:** None. **J. Devia:** None. **L. Botelho:** None. **R.J. Post:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.08/II8

Topic: H.03. Motivation

Support: NIH Grant MH132136.

Title: Mild Traumatic Brain Injury Differentially Alters Paraventricular Nucleus of the Thalamus Pathways to Nucleus Accumbens and Central Amygdala in Mice

Authors: O. RUJAN[1], E. THOMAS[2], W. FLERLAGE[3], B. M. COX[4], *F. S. NUGENT[5]; [1]Pharmacol., Uniformed Service Univ. of Hlth. Sci., Bethesda, MD; [2]Uniformed Services Univ., Bethesda, MD; [3]Pharmacol., Uniformed Services Univ. of Hlth. Sci. Grad. Program In Neurosci., Bethesda, MD; [4]Pharmacol., Brian Cox, Rockville, MD; [5]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Mild traumatic brain injury (mTBI) is a major public health concern, frequently leading to long-term mood disorders such as depression, anxiety, and PTSD. This chronic pathology is linked to dysfunction in affective circuits, including the paraventricular nucleus of the thalamus (PVT). The PVT modulates goal-directed behaviors driven by negative stimuli via distinct projection pathways to the nucleus accumbens (PVT→NAc) and central amygdala (PVT→CeA). Here, we utilized a translationally relevant closed-head injury model of mTBI in mice associated with mood-related deficits to investigate the sex-, cell-type-, and projection-specific effects of mTBI on these stress pathways, focusing on corticotropin-releasing factor-expressing (PVT^{CRF}) neurons. Using retrograde viral tracing in CRF-Cre male and female mice, we found that a greater proportion of PVT^{CRF} neurons project to the NAc than to the CeA. RNAscope analysis revealed that all PVT^{CRF} neurons express VGLUT2, while a minority co-labeled with vGAT, GAD2, or both, with no sex differences. One month post-injury, whole-cell patch-clamp recordings revealed profound pathway-, cell-type-, and sex-specific alterations in intrinsic excitability and excitation/inhibition (E/I) balance. In males, mTBI selectively reduced the intrinsic excitability of overall PVT→CeA neurons without altering spontaneous E/I balance, pointing to an intrinsic plastic mechanism, while leaving the PVT→NAc pathway unchanged.

Conversely, mTBI increased the intrinsic excitability of PVT^{CRF} neurons projecting to both targets. However, while the PVT→NAc increase was driven by intrinsic plasticity, the PVT^{CRF}→CeA hyperexcitability coincided with an E/I shift toward inhibition, suggesting a compensatory response. In females, mTBI increased the overall excitability of both pathways; the PVT→NAc increase was driven by an E/I shift toward excitation, whereas the PVT→CeA increase appeared to be a homeostatic response to a baseline decrease in E/I balance. Strikingly, when isolating PVT^{CRF} neurons in females, mTBI increased the activity of the PVT^{CRF}→NAc pathway (driven by intrinsic plasticity) but *decreased* the excitability of the PVT^{CRF}→CeA pathway. Collectively, these data demonstrate that mTBI induces a convergent intrinsic hyperexcitability within the PVT^{CRF}→NAc pathway across both sexes, highlighting a potential common neuroplastic substrate underlying post-injury behavioral deficits.

Disclosures: O. Rujan: None. **E. Thomas:** None. **W. Flerlage:** None. **B.M. Cox:** None. **F.S. Nugent:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR281.09/II9

Topic: H.03. Motivation

Support: NIH R01-MH133608

Title: The acute and chronic effects of chronic restraint on reward-motivated action selection in mice.

Authors: *C. NOWAK, M. L. WALLACE;
Anat. & Neurobio., Boston Univ. Sch. of Med., Boston, MA

Abstract: Background: Decision-making requires flexible adaptation to changing environmental contingencies. The neural circuits underlying behavioral flexibility, especially under stress, remain incompletely understood. Here, we examined how chronic restraint (CR) stress affects decision-making strategies and *in vivo* bulk calcium (Ca^{2+}) fluorescence and serotonin binding in mice performing a reward-motivated probabilistic switching task. **Methods:** Mice performed a probabilistic switching task with variable reward probabilities across distinct blocks. Mice in the experimental condition (CR) were chronically restrained during a specific task epoch (During-CR), while controls received no intervention. We analyzed trial-by-trial choices, switch probabilities, port preferences, and inter-trial intervals (ITIs) using mixed-effects models accounting for session-level and mouse-level variance. *In vivo* fiber photometry was recorded during behavior. **Results:** CR significantly altered decision dynamics. During CR, CR mice showed (1) reduced switch probability compared to controls (pSwitch), suggesting increased behavioral rigidity; (2) increased inter-trial intervals (ITI); and (3) these effects persisted into the post-CR period, indicating lasting modulatory effects. History-dependent

decision patterns were altered, indicating that decision flexibility was affected. CR inverted Ca^{2+} reward signaling in the During-CR period.

Disclosures: C. Nowak: None. **M.L. Wallace:** None.

Poster

PSTR281: Stress, Adversity, and Negative-State Modulation of Reward Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR281.10/II10

Topic: H.03. Motivation

Support: NIDA Grant DA060221
NIDA Grant T32 DA007287

Title: The fundamental relationship between frustration and motivation: dopamine in the nucleus accumbens shell during satiety-based devaluation

Authors: *Y. MARMOL CONTRERAS[1], A. K. THOMAS[1], D. A. FREEMON[2], P. SHAH[1], T. A. GREEN[1];
[1]Pharmacol. and Toxicology, Univ. of Texas Med. Br. (UTMB), Galveston, TX; [2]Human Pathophysiology and Translational Med., Univ. of Texas Med. Br. (UTMB), League City, TX

Abstract: Frustration has the biological function of deterring behaviors that are no longer beneficial. This function has profound consequences for motivation related behavior and motivation-related neuropsychiatric disorders. Despite the close link between frustration and motivation-related behavior, we know little about the mechanisms that couple frustration to motivation. We recently developed a method for monitoring motivation- and frustration-related behavior simultaneously by measuring duration of bar pressing during operant tasks. We applied this tool to assess whether satiety-based devaluation of a sucrose reward (i.e. low motivation conditions) affect frustration-related behavior. When animals underwent devaluation, they had higher duration of bar pressing, consistent with increased frustration-related behavior. In this study, we expand these findings by injecting animals with the dopamine sensor GRAB-DA and implanting animals with optical fibers. We evaluated the effect of devaluation on dopamine signals at different contingency requirements and reward sizes. Overall, we find that devaluation decreases the amplitude of dopamine signals following pellet consumption, which may be related to frustration.

Disclosures: Y. Marmol Contreras: None. **A.K. Thomas:** None. **D.A. Freemon:** None. **P. Shah:** None. **T.A. Green:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.01/II11

Topic: H.08. Drugs of Abuse and Addiction

Title: Perinatal Fentanyl Exposure Impairs Nucleus Accumbens Metabolism and Downregulates Mitochondrial Biogenesis and Morphology Regulators

Authors: *C. FLORES;
Univ. of Baltimore, Baltimore, MD

Abstract: Perinatal fentanyl exposure (PFE) produces long lasting neurobehavioral consequences in offspring, yet the cellular mechanisms underlying these effects remain unclear. The nucleus accumbens (NAc) is critical for reward processing, and its medium spiny neurons (MSNs) depend on mitochondrial metabolism to support dendritic and synaptic function. The two major MSN populations have opposing behavioral roles: D1 MSNs promote reward seeking, whereas D2 MSNs promote avoidance. Preliminary evidence from our PFE model indicates downregulation of mitochondrial related genes, suggesting impaired metabolic capacity. We hypothesize that PFE disrupts mitochondrial biogenesis and metabolic function in the adolescent NAc, contributing to alterations in neuronal and mitochondrial morphology.Male and female C57BL/6J mice were used, and adolescent offspring were assessed at postnatal day 35 (P35). Dams received fentanyl in drinking water from gestation through postnatal day 21. Mitochondrial function was measured using a Seahorse respiration assay to assess complex specific respiration. Western blotting and qPCR quantified mitochondrial biogenesis markers and morphology related genes. Cell type specific TFAM expression in D1 and D2 MSNs was measured using RNAscope.PFE significantly reduced complex II-dependent respiration, indicating selective impairment of mitochondrial metabolic function. TFAM protein levels were decreased in the NAc, consistent with reduced biogenesis markers at the mRNA level. DRP1 mRNA was also downregulated, suggesting potential alterations in mitochondrial morphology pathways. Cell type specific analysis revealed that TFAM expression was reduced in both D1 and D2 MSNs, indicating broad vulnerability across MSN subtypes.These findings demonstrate that PFE disrupts mitochondrial biogenesis and selectively impairs complex II-driven respiration in the adolescent NAc. Reduced TFAM across MSN subtypes suggests widespread mitochondrial vulnerability that may contribute to structural and functional deficits. Ongoing work will test whether manipulating mitochondrial regulators—such as enhancing TFAM dependent biogenesis or normalizing morphology related markers (such as DRP1)—can rescue metabolic impairments and restore MSN structural integrity.

Disclosures: C. Flores: None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.02/II12

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA054905
F31DA062453

Title: The impact of perinatal fentanyl on dopamine neuron circuitry and behavior

Authors: *J. M. MCINERNEY[1], J. OLUSAKIN[1], M. LUJÁN[2], B. QAMAR[1], S. HAJIRNIS[1], A. KASHYAP[1], J. F. CHEER[1], M. LOBO[1];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Anat. and Neurobio., Univ. of Illinois Chicago, Col. of Med., Chicago, IL

Abstract: Use of illicit substances has reached endemic levels in the United States with over 91,000 deaths due to drug overdose occurring in 2020. This has largely affected women of childbearing age as opioid use disorder has more than quadrupled among pregnant women in the past 20 years. Both clinical and preclinical studies show that opioid exposure during gestation can lead to developmental delays, cognitive impairment, anhedonia and altered motivation in offspring. Opioids induce neuroadaptations in the mesolimbic dopamine pathway, which is largely implicated in reward. The pathway originates in the ventral tegmental area (VTA) where dopamine neurons project to the nucleus accumbens (NAc) and Prefrontal Cortex (PFC). How perinatal opioid exposure, including the highly potent synthetic opioid fentanyl impacts the transcriptional landscape throughout the development of the mesolimbic dopamine pathway as well as the lasting effect on motivation requires further investigation. Differential gene expression analysis of the PFC, NAc, and VTA across early development into adolescence (P1, P7, P14, P21 and P35) revealed perinatal fentanyl exposure (PFE) induces significant alterations in expression patterns of several genes important for neuronal maturation and axonal guidance, including transcription factors critical for dopamine neuron development during the juvenile time period. In addition, PFE mice exhibit increased seeking for natural reward in adolescence and altered dopamine dynamics during increased response requirements in adulthood measured through a sucrose operant task. These results indicate that perinatal fentanyl exposure and subsequent abstinence produce lasting transcriptional, and behavioral effects on the development and function of the mesolimbic dopamine pathway.

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Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.03/II13

Topic: H.08. Drugs of Abuse and Addiction

Support: Williams College

Title: Buprenorphine treatment modulates pain responses in an age-specific manner in a mouse model of neonatal opioid withdrawal syndrome

Authors: F. HIDALGO GONCALVES, *S. A. ROBINSON;
Williams Col., Williamstown, MA

Abstract: Buprenorphine is being increasingly used to treat neonatal opioid withdrawal syndrome (NOWS), yet whether it provides lasting benefits beyond acute withdrawal management remains unknown. To investigate this, we used a third-trimester equivalency mouse model of early life morphine exposure, in which male and female C57BL/6J mouse pups were administered saline or morphine (10 mg/kg) from postnatal day (PND) 1- 14 and co-administered buprenorphine (BPN) (0.3 mg/kg) from PND 12-14 (n = 10-14/group). We found that BPN co-administration attenuated morphine-induced thermal hyperalgesia on PND 15 ($p < 0.0001$), but did not significantly affect baseline nociception or morphine-induced alterations in analgesic efficacy when measured during adolescence (PNDs 34-41). Gene expression analysis in the prefrontal cortex revealed a modulation of proinflammatory markers during adolescence that was absent in neonatal tissue; morphine-exposed animals exhibited increased TNFα mRNA expression compared to saline controls ($p < 0.05$), and morphine/buprenorphine treated animals exhibited TLR4 downregulation relative to all other groups ($p < 0.001$). Furthermore, preliminary data from c-Fos immunostaining following a noxious thermal stimulus revealed a trend toward suppression of morphine-driven neuronal activity across the nucleus accumbens, periaqueductal gray, and medulla. Altogether, these findings demonstrate that neonatal morphine exposure induces lasting alterations in pain-induced neuronal activity and immune signaling, independent of early BPN treatment.

Disclosures: F. Hidalgo Goncalves: None. **S.A. Robinson:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.04/II14

Topic: H.08. Drugs of Abuse and Addiction

Support: VA Merit Review BX006167

Title: Novel cyclized glycosylated endomorphin analog A2 provides highly effective inhibition of pain signaling (antinociception) with reduced respiratory depression relative to morphine in male and female rats.

Authors: *L. FERREIRA NAKATANI[1], J. E. ZADINA[2];
[1]Tulane Univ., New Orleans, LA; [2]Dept of Medicine/Neurosci Lab. #8516, Tulane Univerity Sch. of Med/SE LA Veterans Hlth. Care Syst., New Orleans, LA

Abstract: Mu-opioid receptor (MOR) agonists remain the gold standard for management of moderate to severe pain, but their clinical use is limited by adverse effects, including respiratory depression. We previously showed that a cyclized analog of EM1 (ZH853), at doses providing equal or greater antinociception than morphine, produced less respiratory depression. Here we test a novel lead glycosylated cyclic analog (A2), that has shown significantly increased antinociception relative to morphine and ZH853, for its respiratory effects in male and female rats. A2 at 1.8mg/kg produced antinociceptive duration equivalent to 10mg/kg morphine (~2h) while 3.2 and 5.6 mg/kg A2 produced increasingly greater duration (up to *3.6h*). These doses were chosen for comparison in respiratory tests. Whole-body plethysmography revealed that morphine produced rapid ~50% inhibition of Minute Ventilation (MV) 1 min after injection, and scores were significantly below vehicle during the 0-20-minute post-injection period. In the 30-60-minute time frame, males and females recovered to an average of 8% and 22% inhibition, respectively. By contrast, A2 produced complex biphasic dose-and time-dependent responses. The low dose (1.8) showed small (ns) decreases in the first 30 min, but small increases in the later (30'-60') period. The high dose (5.6) showed small inhibitory effects across the time course. The intermediate (3.2) dose produced respiratory *increases*, particularly for males. In general, females showed greater (ns) inhibition at the high dose, while males showed greater, significant increases in respiration with the intermediate dose. In the 30-60-minute time frame, males and females given the 3.2 dose showed an average increase in respiration of 17% and 30% respectively. Together, these findings suggest that A2 provides prolonged antinociceptive efficacy with substantially attenuated respiratory suppression relative to morphine. Additionally, the unique ventilatory profile of A2 suggests differential effects on one or more of the complex respiratory mechanisms that are inhibited by classical opioid agonists.

Disclosures: L. Ferreira Nakatani: None. **J.E. Zadina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JEZ is an 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

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.05/II15

Topic: H.08. Drugs of Abuse and Addiction

Support: R01 DA050871
T32DA07287
F30DA065327
John S. Dunn Research Foundation
Chauncey Leake Distinguished Professorship
Center for Addiction Sciences and Therapeutics

Title: In Utero Opioid Exposure Alters Neurodevelopment and Behavior in a Murine Model of Medication for Opioid Use Disorder

Authors: *J. TIERNEY[1], C. R. MERRITT[2], K. TRINH[5], J. GRANCHI[3], S. A. BUFFINGTON[6], K. A. CUNNINGHAM[2], P. WU[4];
[2]Ctr. for Addiction Res., [1]Univ. of Texas Med. Br., Galveston, TX; [3]Univ. of Texas Med. Br., Seabrook, TX; [4]Dept Neurosci/Cell Biol, Univ. of Texas Med. Br., League City, TX; [5]Univ. of Texas Med. Br. at Galveston, Galveston, TX; [6]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Maternal opioid use disorder (OUD) diagnoses increased 131% and neonatal abstinence syndrome rose 82% from 2010 to 2017. Managing pregnant OUD patients with buprenorphine (BUP) requires balancing maternal stability against potential opioid-evoked developmental defects. Our previous work discovered that dams treated with oxycodone (OXY) pre-pregnancy and BUP during gestation (OXY+BUP) resulted in abnormal brain neurogenesis and sex-dependent behavioral sequelae in offspring. Here we tested the hypothesis that OXY+BUP alters neurogenesis at embryonic day (E) 13.5 and elicits altered behavioral sequela in adolescent offspring. C57BL/6J dams were treated with saline or OXY (40 mg/kg; p.o., 7 days) pre-mating. Post-copulation OXY continued or was switched to BUP (0.5-4 mg/kg p.o, ramping) to model OUD management in pregnancy. Embryos were collected at E13.5 for immunohistochemistry and single cell spatial transcriptomics in the medial prefrontal cortex (mPFC) and insula (IC). Offspring behavior was assessed via elevated plus maze (EPM), sucrose preference test (SPT), and novel object recognition (NOR) on postnatal day 60. OXY+BUP exposure *in utero* impacted neurodevelopment in a sex-dependent manner. At E13.5, both males and females showed an increase in SATB2+ cells in the IC ($F_{2,18}$=10.80, p=0.0008; n=3-5). Females, but not males, additionally displayed increased CTIP2+ cells in the mPFC ($F_{2,17}$=8.003, p=0.0036; n=3-5). In the IC, females also showed a trend for increased nociceptin opioid receptor transcripts following OXY+OXY and OXY+BUP exposure. Behaviorally, there was a significant main effect of drug, which decreased time spent in the open arms of the EPM (F2,70=5.723, p=0.0050; n=12-16), decreased sucrose preference (F2,68=6.550, p = 0.0025; n=11-15), and impaired recognition memory compared to control. These effects were most apparent in OXY+OXY-exposed male offspring (p =0.027) in the EPM, OXY+BUP-exposed female offspring (p=0.0007) in SPT, and in females exposed to OXY+OXY (p=0.054) and OXY+BUP (p=0.078) in NOR. Our data suggest that maternal opioid exposure impacts early neurodevelopment and adolescent behaviors differentially based on sex. Ongoing research aims to clarify the impact of OXY and BUP on brain and behavior across developmental stages.

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Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.06/II16

Topic: H.08. Drugs of Abuse and Addiction

Support: Student Awards for Research & Creativity - Summer Program

Title: Examining the Short and Long-Term Impact of Chronic Ketamine Exposure in Adolescent Mice

Authors: *S. ARENAS[1], S. BATES[2];
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Abstract: Ketamine belongs to the dissociative class of drugs. Ketamine also has addictive potential, and repeated administration can produce sensitization of locomotor effects. It is also abused among adolescents, yet the impact of chronic ketamine use during this developmental period remains unclear. Chronic long-term use of ketamine has been shown to increase locomotor activity in male rats, yet little is known about its effects in mice. Additionally, most work has focused on males, which leaves out the sex differences. This study examines the short and long-term effects of ketamine in male and female adolescent mice. Additionally, the study examines cross-sensitization to cocaine. This includes a seven-day period of injections with locomotor testing on days 1 and 7. Afterwards, there is an abstinence period. Then, on day 30, they are injected with ketamine again, and their locomotor activity is assessed. A week later, we injected the mice with cocaine to observe if chronic ketamine exposure increases the behavioral response to cocaine. Preliminary results suggest that ketamine does lead to locomotor sensitization in adolescent mice, with a greater effect in females. It is important to understand the effects of ketamine in adolescence, both short- and long-term, as they provide us with insight regarding drug interactions with the developing brain and its long-term consequences, adding to the limited knowledge we have on this topic.

Disclosures: S. Arenas: None. **S. Bates:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.07/II17

Topic: H.08. Drugs of Abuse and Addiction

Support: Adolescent Brain and Cognitive Development Study

Title: Sex differences in predicting adolescent substance use

Authors: *M. J. DAY;
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Abstract: Introduction: Substance use disorders (SUDs) are a leading cause of preventable morbidity among adolescents. Sex differences exist in the prevalence, onset, and neurobiology of cannabis, nicotine, and alcohol use, yet most predictive models do not distinguish between males

and females. Whether sex-stratified models reveal divergent predictive architectures has implications for sex-sensitive prevention. Methods: Using baseline data (ages 9-10) from the ABCD Study (v7.0, N = 8,491), elastic-net logistic regression models were fit separately in boys (N =4,446, 52.4%) and girls (N =4,04547.6%) using 666 multimodal features: structural neuroimaging (sMRI), CBCL behavioral and emotional scales, KSADS psychiatric symptoms, adverse childhood experiences (ACEs), socioeconomic status (SES), polygenic scores, and family history of substance use. Heavy use (≥20 days in the 365 days before the year-7 visit) was the binary outcome for cannabis, nicotine, and alcohol. Performance was estimated via nested cross-validation, and AUC was the primary metric. Beta weights were averaged across folds to compare feature importance by sex. Results: Model performance was statistically similar between sexes across substances and outcome thresholds (permutation tests, all $p > 0.20$). Mean fold AUCs for heavy use were: cannabis (girls=0.639, boys=0.621), nicotine (girls=0.678, boys=0.626), and alcohol (girls=0.520, boys=0.533). Feature importance diverged by sex. 8 of the top 15 cannabis features were shared but with an inverted rank ordering (Spearman $\rho = -0.71$, $p = 0.046$): girls' risk was anchored by family environment (non-biological family history, $\beta = 0.075$; CBCL rule-breaking, $\beta = 0.054$), while boys' risk was anchored by externalizing symptoms (ODD symptom count, $\beta = 0.070$; trauma exposure, $\beta = 0.046$). Divergence was greater for nicotine (4 of 15 features shared) and complete for alcohol (0 of 15 features shared). Girls' top predictors were neuroimaging and anxiety symptoms, and boys' was OCD diagnosis ($\beta = -0.302$). Conclusions: Sex-stratified models achieved statistically equivalent predictive performance, yet the risk features diverged. Girls' risk was linked to family and externalizing behavior; boys' risk was symptom-specific, with externalizing, trauma, and neurobiological features. Divergence was substance-specific and most striking for alcohol. These findings suggest that homogeneous models obscure meaningfully different neurodevelopmental pathways. These divergent risk architectures are identifiable at ages 9-10 and predictive of heavy use ~7 years later, underscoring the value of sex-stratified approaches for early, targeted prevention.

Disclosures: M.J. Day: None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.08/II18

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA grant U01DA051993
Institute for Mental Health Resaerch
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Arizona Department of Health Services (ADHS) and the state of Arizona (ADHS Grant No. CTR057001)

Title: Investigating the behavioral and neurobiological effects of oxycodone across the lifespan

Authors: *O. LAW[1], J. C. GEWIRTZ[2], J. L. VERPEUT[3];
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Abstract: Withdrawal following repeated opioid exposure produces negative affective signs (e.g., anxiety, anhedonia) and reduced sociality. Similar long-term effects have been reported in rats exposed to opioids in utero. We are interested in investigating whether similar or distinct mechanisms underly the similar behavior and mood state following prenatal and adult opioid exposure. We first examined the effects of spontaneous withdrawal from repeated oxycodone administration in adult C57Bl/6J mice (30 mg/kg/day for 10 days). Now, to investigate how maternal oxycodone exposure impacts offspring, we have exposed pups to oxycodone (15 mg/kg/day) through gestation and postnatally until postnatal day 14 (P14). Social preference in adults was measured using the three-chamber task and group social interactions were analyzed using an open field. While no differences in social preference were found, oxycodone-withdrawn mice participated in fewer total social behavior events in the group social test during withdrawal compared to their baseline values ($p < 0.001$). Specifically, nose-to-body interactions appear to be driving this change ($p < 0.001$). Next, anxiety-like behavior was tested using the marble burying task. Oxycodone-withdrawn mice buried significantly fewer marbles ($p = 0.003$), potentially indicating anhedonia. Changes in oligodendrocyte expression in the prefrontal cortex (PFC) was revealed using RT-qPCR. Of the five examined oligodendrocyte-related genes, *Tcf7l2* ($p < 0.01$) and *Klk6* ($p = 0.045$) showed decreased expression in oxycodone mice relative to control, suggesting a potential deficit in oligodendrocyte functioning. From P1-P14, oxycodone-exposed pups showed increased body weight ($p = 0.03$) and grasped earlier ($p < 0.001$), but showed no differences in righting behavior. Currently, offspring are being tested for changes in social preference, anxiety-like behavior, reward and motivated behavior, and cognition. Following the behavioral tasks, tissue will be collected for immunohistochemistry of the nucleus accumbens, ventral tegmental area, and PFC. Taken altogether, these studies will help us gain a more comprehensive understanding of the behavioral and neurobiological effects of oxycodone exposure and withdrawal across multiple stages of development.

Disclosures: O. Law: None. **J.C. Gewirtz:** None. **J.L. Verpeut:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.09/II19

Topic: H.08. Drugs of Abuse and Addiction

Support: CIC-UMSNH 18096
CIC-UMSNH 18146
CIC-UMSNH 18099

Title: Acute toluene exposure modifies cardiovascular alpha-1D adrenergic response in rats

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[1]Facultad de Quimico Farmacobiologia, [2]Inst. de Investigaciones Quimico Biologicas, [3]Facultad de Atencion Integral en Ciencias de la Salud y Asistencia Social, [4]Facultad de Ciencias Medicas y Biologicas "Dr. Ignacio Chavez", Univ. Michoacana de San Nicolas de Hidalgo, Morelia, Mexico; [5]Ingenieria Quimica y Bioquimica, TecNM/Campus Morelia, Morelia, Mexico

Abstract: Inhalants are volatile substances of diverse chemical nature that share a common route of administration and represent a global public health problem. Toluene is the most commonly misused recreational inhalant; it acts as a central nervous system depressant and produces psychoactive effects. Furthermore, it is readily available and is found in inexpensive and legally accessible household products, making it a common drug of initiation among adolescents. In the cardiovascular system, toluene increases blood pressure and induces arrhythmias, tachycardia, catecholamine sensitization, and sudden sniffing death; however, the mechanisms of action involved in these effects are unknown. The aim of this study was to investigate if acute toluene exposure modifies the cardiovascular adrenergic response in anesthetized rats. Male Wistar rats (300-400 g) were acutely exposed to toluene (6000 ppm) or to air (control). Animals underwent a single 30-minute exposure in static chambers. Subsequently, the animals were anesthetized, and dose-response curves were generated for phenylephrine (an alpha-1 adrenergic agonist) in the absence and presence of dapiprazole (an alpha-1D adrenergic antagonist). The results showed that acute toluene exposure decreases diastolic blood pressure without affecting systolic blood pressure. To evaluate the involvement of alpha-1D adrenergic receptors, dose-response curves were constructed in the presence and absence of dapiprazole. Acute toluene exposure reduced the contribution of alpha-1D adrenergic receptors to the regulation of diastolic blood pressure, without modifying systolic blood pressure compared with the control group. Heart rate was not changed by acute toluene exposure. In conclusion, our results suggest that acute toluene exposure modifies cardiovascular alpha-1D-mediated adrenergic response.

Disclosures: J. Salvador Alvarez: None. **D. Godinez-Hernandez:** None. **C. Aguilar-Carachure:** None. **L.F. Ortega-Varela:** None. **A. Aguilera-Méndez:** None. **C.J. Gutierrez-Garcia:** None. **M.Y. Gauthereau-Torres:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.10/II20

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA DA047976

Title: The effect of social odor choice on heroin craving

Authors: *K. PAPASTRAT[1], Z. HUANG[1], L. A. RAMSEY[2], M. VENNIRO[3];
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Abstract: Background: We previously demonstrated that familiar social odors attenuate the incubation of cocaine craving in both male and female rats. In the present study, we examined the generalizability of this effect in rats with a history of heroin self-administration by assessing social odor versus heroin preference and the impact of social odors on the incubation of heroin craving. In addition, we investigated neuronal activation during heroin craving following social odor-induced abstinence compared with forced abstinence. **Methods:** We trained male and female rats first on social odor self-administration and then on heroin self-administration. We then assessed relapse to drug seeking under extinction conditions after 1 and 15 abstinence days. Between test days, we trained rats on voluntary abstinence through a choice paradigm between social odor and heroin or forced abstinence in their home-cage. Finally, we analyzed whole-brain Fos expression following test day 15. **Results**: Regardless of sex, rats consistently chose social odors over heroin during voluntary abstinence, and this preference attenuated incubation of heroin craving relative to the robust incubation observed following forced abstinence. Brain-wide analyses of Fos expression identified activity in brain regions associated with the expression of incubated heroin craving. **Conclusion**: We found that social odor's role in incubation of cocaine craving after voluntary and forced abstinence generalizes to male and female rats with a history of heroin self-administration. These results highlight the potential for odor-based social sensory interventions for treating substance use disorders and provide new insight into the brain regions activated during heroin craving in rats.

Disclosures: K. Papastrat: None. **Z. Huang:** None. **L.A. Ramsey:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.11/II21

Topic: H.08. Drugs of Abuse and Addiction

Support: Matthew Osborne Research Fellowship
NIDA Grant R01DA056440
NIDA Grant R01DA063051

Title: Central amygdala activity mediates the protective effect of social volitional abstinence on incubation of drug craving

Authors: *S. J. WEBER[1], M. VENNIRO[2];
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Abstract: Central amygdala neuronal activity mediates the protective effect of social reward on incubation of drug craving
Sophia J. Weber[1,2], Shannon E. Kirk[1], Clara J. Harvey[1], Danielle Choi[1], Max Schain[1], Marco Venniro[1,2,3]
Affiliations:1Department of Neurobiology, University of Maryland School of Medicine, Baltimore USA 2Kahlert Institute for Addiction Medicine, Baltimore USA 3Department of Psychiatry, University of Maryland School of Medicine, Baltimore USA
Background Relapse represents a consistent clinical problem in the treatment of substance use disorders. The incubation of drug craving model can emulate similar behavior in rodents, with rats showing elevated drug-seeking when tested after prolonged abstinence from drug self-administration. We can reduce incubated drug-seeking by allowing rats to voluntarily suppress their intake of drug in a choice paradigm because of their preference for social reward. We investigated calcium transients in the Central Amygdala (CeA) during drug seeking after social-volitional and food-volitional abstinence.
Methods First, we injected GCaMP8s in CeA and a fiber optic cannula was implanted along with an intravenous jugular catheter. We then trained male (M) and female (F) rats to lever press to receive 60 s of social interaction (2 h/d x 5 d) and then intravenous methamphetamine (0.1 mg/kg/infusion; 6 h/d x 10 d). We performed drug-seeking tests on abstinence day (AD) 1 and AD15. Between these tests half of the rats were run on a choice procedure in which they were offered two levers, one for alternative reward, social interaction or food pellet, and one for drug (15 trials/d X 13 d), while the other half remained in their home cage.
Results Our initial results indicate a significant difference in CeA calcium transients time locked to lever press for reward when comparing food and social behavior. Drug seeking behavioral data trended towards a significant effect of test day when analyzing active lever presses. Furthermore, area under the curve (AUC) for CeA calcium showed significant effects of both test day and behavioral group with a trend towards a test day x group interaction.
Conclusions Our data indicates that CeA activity in response to drug-associated cues may be increased during incubated drug seeking.

Disclosures: S.J. Weber: None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.12/II22

Topic: H.08. Drugs of Abuse and Addiction

Support: 5R01MH129310-04

Title: Social isolation induces coordinated changes in social motivation and the peripheral immune-transcriptome

Authors: *A. PACHECO-SPIEWAK[1], Z. HUANG[1], K. PAPASTRAT[1], Y. LAI[2], M. VENNIRO[3];
[1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Univ. of Maryland, Baltimore, Baltimore, MD; [3]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Background: Societal connectivity is known to be integral for maintaining psychological well-being but has also been reported to affect physical health and immunity. This suggests that the peripheral immune system is affected by, and potentially contributes to, behavioral changes during social interactions. Here, we used social isolation as a paradigm to dissect the molecular pathways underlying such connectivity. **Methods:** We weaned rats at post-natal day 21 into socially isolated (1 rat/cage) or socially housed (2 rats/cage) conditions for 3 days (acute isolation) or 5 weeks (chronic isolation). We then used a lever-press counter to measure changes in their motivation for food or peer social interactions. In parallel, we measured changes in peripheral immune cells using spectral cytometry and single-cell RNAseq. **Results:** Regardless of sex, acute and chronic social isolation increased social motivation, without affecting motivation for food. Although the overall cellularity of different immune populations was unchanged, social isolation significantly altered multiple gene expression profiles in peripheral cells. A major perturbation in isolated animals was in signaling molecules in the NF-κB pathway. At the acute time point, we identified numerous cell types contributing to this signature, whereas at the chronic time point, the contribution was largely limited to neutrophils and classical monocytes. We found TNF, an upstream driver of NFkB, could be targeted to partially modulate increased social motivation of socially isolated rats. **Conclusion:** Our data suggests multifactorial feedback from specific subsets of circulating peripheral immune cells can directly impact the behavioral adaptation to social isolation.

Disclosures: A. Pacheco-Spiewak: None. **Z. Huang:** None. **K. Papastrat:** None. **Y. Lai:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.13/II23

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA [DA047976]
NIDA [DA056440]
NIMH [129310]

Title: Behavioral modeling of social rejection induced heroin craving

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Abstract: BACKROUND: Social support promotes recovery during abstinence, yet the role of social peers in regulating drug use remains poorly understood. We developed a model showing that passive or voluntary heroin exposure alters social interactions and increases subsequent heroin craving.
METHODS: We trained male and female rats to self-administer food and mutual social reward (1 h/day, 5-sessions), passively exposed resident rats to heroin via osmotic minipumps (3.5 mg/kg/day) and then assessed choice between food and mutual social reward (15 trials/day, 5-sessions), with partner lever pressing providing access to social interaction. In a separate cohort, we trained resident rats to self-administer heroin (0.5 mg/kg/infusion; 6 h/day, 14-sessions) and tested early relapse. We then assessed their choice between mutual social interaction and heroin (15 trials/day, 14-days) and subsequently tested the incubation of heroin craving.
RESULTS: We found that heroin withdrawal reduced motivation for mutual social interaction. In addition, heroin dependence increased social rejection by partner rats. Moreover, despite being rejected, 67% of resident rats continued to seek social interaction during the choice task. However, prolonged social rejection caused 33% of these rejected rats to shift their preference from social reward to heroin reward. Furthermore, the protective effect of social interaction on drug craving was abolished by social rejection: resident rats that experienced social rejection during voluntary abstinence exhibited greater incubation of heroin craving than their non-rejected counterparts.
CONCLUSION: These findings suggest that volitional social rejection can exacerbate drug craving and highlight the importance of social support as a critical component of recovery.

Disclosures: N. Baidoo: None. **M. Anfuson:** None. **Z. Huang:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.14/II24

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA063051

Title: A novel model of compulsive food-seeking in rats: GLP-1 receptor agonist and social reward as therapeutic interventions

Authors: *Y. LAI[1], N. BAIDOO[2], M. MICIONI DI BONAVENTURA[3], C. CIFANI[4], M. VENNIRO[5];
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Maryland, Baltimore, Baltimore, MD; [3]Univ. of Camerino, Sch. of Pharmacy, Pharmacol. Unit, Camerino, Italy; [4]Sch. of Pharmacy, Pharmacol. Unit, Univ. of Camerino, Camerino, Italy; [5]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Background Compulsive food-seeking is the core behavioral pathology of binge-eating disorder and obesity. Here, we developed a compulsive food-seeking model and investigated two therapeutic strategies: GLP-1 receptor agonists (GLP-1 RAs), a promising pharmacological approach targeting both central and peripheral mechanisms, and social interaction, a behavioral intervention shown to be protective against mental disorders, as an alternative reward competing with compulsive food-seeking. Methods We trained male and female rats to lever press for palatable food under either continuous or intermittent access schedule to induce binge-like behavior. We used extinction and progressive-ratio tests to assess food motivation and classify binge rats. We then train rats to lever press for 60 seconds of social interaction. Finally, we trained rats to choose between food and social reward. We administered Exendin-4 (EX-4) intraperitoneally prior to food self-administration, progressive ratio, social self-administration, and food versus social choice tests. Results Our findings revealed that ~40% of all rats developed binge-like behaviors. In equal fixed-ratio food vs social choice sessions, the binge rats did not show decreased food preference compared to their non-binge peers. Systemic EX-4 administration reduces lever press for food reward, regardless of binge-like phenotype with the relative food versus social choices remain unchanged by EX4. Conclusions These findings highlight the heterogeneity of binge-like behaviors induced by intermittent access palatable food self-administration and the novel effect of GLP-1 RA on binge-like behaviors as well as social motivation.

Disclosures: Y. Lai: None. **N. Baidoo:** None. **M. Micioni Di Bonaventura:** None. **C. Cifani:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.15/II25

Topic: H.08. Drugs of Abuse and Addiction

Support: 5R01MH129310

Title: Social motivation impairments in rat models for autism spectrum disorder

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Abstract: Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts social interaction. Here, we investigated how mutations in commonly associated genes (FMR1, GRIN2B, and NRXN1) affect volitional social interactions in rat models, and whether acute or chronic social isolation modulates these effects in FMR1 rats **Method**: Wild-type and ASD-risk mutant rats were trained for food and social self-administration across increasing fixed-ratio requirements and progressive-ratio testing. We also tested a mutually exclusive choice procedure between food and social interaction. Additionally, we tested separate FMR1 cohorts after either 3 days or 5 weeks of social isolation, with effort requirements extended through higher fixed-ratio schedules. **Results**: Most ASD-risk genotypes did not show consistent reductions in social responding. FMR1 homozygous knockout rats showed modest reductions in social reward seeking but still shifted from food toward social reward when food effort increased, indicating preserved social reinforcement. In additional FMR1 cohorts, 3 days of isolation increased low-effort social responding, but deficits emerged at higher fixed-ratio requirements. After 5 weeks of isolation, social motivation deficits were more pronounced than wild-type controls. **Conclusion**: Together, these findings suggest that reduced social motivation is not a broad feature of ASD-risk rat models, but that FMR1 disruption may confer a specific vulnerability to disrupted social reward seeking under isolation and increased-effort conditions.

Disclosures: J. White: None. **A. Pacheco-Spiewak:** None. **K. Papastrat:** None. **A. Casile:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

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Program #/Poster #: PSTR282.16/II26

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA047976
NIDA Grant DA056440
NIMH Grant MH129310
NIA R24AG065172

Title: Cerebellar circuits mediating social craving

Authors: *Z. HUANG[1], A. PACHECO-SPIEWAK[1], C. LIS[2], K. PAPASTRAT[1], A. CASILE[3], S. J. WEBER[4], C. LENA[5], L. A. RAMSEY[6], M. VENNIRO[7];
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Abstract: Background: Social interactions are highly rewarding, and social isolation enhances motivation for social engagement in humans. Here, we developed a rat model to mimic social craving and identified novel roles for cerebellar circuits in mediating social craving.**Methods**: First, we trained male and female rats for food (2h/d, 6d) and social (2h/d, 12d) self-administration. Next, we assessed social craving following 1 and 14 days of isolation. We used neuronal activity marker Fos to identify cerebellar circuits activated by social craving. Using chemogenetic approaches, we investigated the causal role of these regions during social craving. Lastly, we used *ex vivo* brain slice electrophysiology to examine glutamatergic synaptic plasticity within cerebellar circuits following social isolation.**Results**: Regardless of sex, social craving was higher after 14 days of isolation compared to 1 day of isolation, demonstrating enhanced social craving following social deprivation. Social craving was associated with elevated Fos expression in the deep cerebellar nuclei (DCN), upstream cerebellar Vermis Lobule VI and Crus I, and downstream ventromedial/lateral thalamus (VML). Chemogenetic inhibition of DCN, Crus I, VML and DCN◊VML pathway decreased social craving after 14 days of isolation. Operant social training induced glutamatergic synaptic plasticity in DCN◊VML neurons, characterized by increased NMDAR-mediated transmission and greater silent synapse prevalence after 1 day of isolation. Glutamatergic synaptic plasticity returned to baseline levels after 14 days of isolation.**Conclusion**: We introduced a novel social craving rat model and identified a role for DCN, Crus I, VML, and DCN◊VML pathway in enhanced social craving following social isolation.

Disclosures: Z. Huang: None. **A. Pacheco-Spiewak:** None. **C. Lis:** None. **K. Papastrat:** None. **A. Casile:** None. **S.J. Weber:** None. **C. Lena:** None. **L.A. Ramsey:** None. **M. Venniro:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

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Program #/Poster #: PSTR282.17/II27

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH grant R03DA059681

Title: Adolescent Social Isolation Reveals a Selective Effect of Oxytocin on Oxycodone Motivation

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Abstract: Adolescent social stress is a significant risk factor for substance use disorders and may increase vulnerability to opioid addiction through persistent alterations in stress and reward circuitry. Oxytocin has emerged as a potential therapeutic target due to its ability to modulate stress responsivity and drug-seeking behavior. The present study examines the effects of

adolescent social isolation on long-term changes in anxiety-like behavior, and oxycodone-taking / -seeking, as well as the ability of acute oxytocin administration to moderate oxycodone-associated behaviors. Male Sprague-Dawley rats were assigned to either social isolation or pair-housed conditions from postnatal day (PND) 35-60 and received little experimenter handling. On PND 61-62, anxiety-like behavior was assessed using the elevated plus maze and light/dark box. Rats were then all housed individually prior to beginning intravenous oxycodone self-administration (0.1 mg/kg/infusion), consisting of six daily fixed-ratio 1 (FR1) sessions followed by six daily FR3 sessions. Motivation for oxycodone was evaluated across five progressive ratio sessions, with oxytocin (15 IU/kg, IP) or vehicle administered 30 min prior to testing. Next, rats underwent instrumental extinction and cue-, drug-, and stress-primed reinstatement tests. Socially isolated rats exhibited increased anxiety-like behavior relative to pair-housed rats, as evidenced by reduced open-arm exploration in the elevated plus maze and decreased exploration of the light compartment in the light/dark box test. Oxytocin reduced oxycodone breakpoint in socially isolated animals, whereas no effect was observed in pair-housed rats. The initial analysis suggests that oxytocin had no effect on cue- or drug-primed reinstatement, with data collection on oxytocin effects on stress-primed seeking and immediate early gene expression in progress. These findings suggest that adolescent social isolation produces enduring behavioral consequences that increase vulnerability to addiction-related phenotypes and that oxytocin may selectively reduce opioid motivation in stress-exposed individuals.

Disclosures: E.A. Colley: None. **L.A. Knackstedt:** None. **M. Schwendt:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

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Program #/Poster #: PSTR282.18/II28

Topic: H.08. Drugs of Abuse and Addiction

Support: RCHSS Internal Research Advancement Fund
OVPR Internal Fund
Murphy Lab Georgia State University

Title: Reproductive experience modulates glutamatergic synaptic transmission in hippocampal and medial prefrontal circuits

Authors: *E. M. POGUE[1], E. HOLLIDAY[2];
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Abstract: Postpartum psychiatric disorders, including postpartum depression (PPD) and postpartum psychosis (PPP), are associated with significant morbidity in mothers and adverse outcomes in offspring (Friedman et al., 2023; Amer et al., 2024). Alterations in glutamatergic signaling have been implicated in mood and psychotic disorders (Jun et al., 2014; Kerner, 2009);

however, the synaptic mechanisms underlying postpartum-related neurobiological changes remain unclear. Reproductive experience (e.g. pregnancy) is being examined for its effects on glutamatergic synaptic function in the hippocampus and medial prefrontal cortex (mPFC) in parous and nulliparous rats. Synaptic receptor composition will be quantified in isolated synaptosomal fractions by Western blot analysis of NMDA receptor subunits (GluN1, GluN2A, and GluN2B) and AMPA receptor subunits (GluA1 and GluA2). Cannabinoid receptor type 1 (CB1R) expression and subcellular distribution may also be assessed to explore potential interactions between reproductive experience, glutamatergic signaling, and endocannabinoid trafficking. Single-channel electrophysiology will be used to assess NMDA and AMPA receptor function by quantifying channel open probability, unitary conductance, and burst kinetics to provide insight into receptor gating mechanisms of individual ion channels. We hypothesize that reproductive experience produces persistent alterations in NMDA and AMPA receptor composition and function and that these adaptations may contribute to long-lasting changes in excitatory synaptic transmission. These studies will provide insight into mechanisms of maternal brain plasticity and may identify synaptic pathways relevant to vulnerability or resilience to postpartum psychiatric disorders.

Disclosures: E.M. Pogue: A. Employment/Salary (full or part-time):; Kennesaw State University. **E. Holliday:** A. Employment/Salary (full or part-time):; Kennesaw State University.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.19/II29

Topic: H.08. Drugs of Abuse and Addiction

Title: The Relationship Between GRIN2A/GRIN2B Genotypes, Trait Anxiety, Adverse Childhood Experiences, Nicotine Use, and Cognitive Functions

Authors: *E. CLARKE[1], E. HOLLIDAY[1], C. PARKER[2], E. POGUE[3];
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Abstract: The current study investigates the relationship between the genotypic expression of the GRIN2 genes, adverse childhood experiences (ACEs), Mental health, nicotine use, and consequences toward cognition. The *GRIN2* genes are implicated in the glutaminergic system's N-Methyl-D-Aspartate (NMDA) receptors and synaptic plasticity (Barros et. al., 2025). While there have been thousands of *GRIN* variants discovered, many mutations are concentrated within the *GRIN2A/GRIN2B* genes (Ugale et. al., 2024). The *GRIN2* genes code for the expression of the *GLUN2* subunit of the NMDA receptor, which is involved in the control of synaptic plasticity and glutamate release within the hippocampus and frontal cortex (Doan et. al., 2023). Given glutamate is the most abundant excitatory neurotransmitter within the brain; this neurotransmitter is inextricably tied to the development of mental health issues, substance use issues, and

cognitive abilities. Variations of the *GRIN2* genes have also been connected to cognitive deficits and depressive symptoms (Karanović et. al., 2025). Previous studies have shown that exposure to life stress and recreational substances like nicotine can potentially induce long-lasting changes in epigenetic patterns, thus providing a possible genetic explanation for the aversive effects (Engdahl et. al., 2021). Fifty-eight female and 28 male college students (M age = 18.63 years) took surveys assessing adverse life experiences (Life Events Checklist; LEC), adverse childhood experiences (Adverse Childhood Experiences Questionnaire; ACEs), substance use (Alcohol, Smoking, and Substance Involvement Screening Test; ASSIST), and state and trait anxiety (State-Trait Anxiety Inventory; STAI-S, STAI-T; Spielberger, et al., 1983). Cognitive flexibility and impulsive decision making were measured using the Number Letter Switch Task (millisecond.com) and the Delay Discounting Task (millisecond.com), respectively. Participants provided a passive drool saliva sample for DNA extraction and analysis of the *GRIN2* gene expression. Data is fully collected; however, salivatory gene analysis is ongoing. It is hypothesized that ACEs and mental health will be related to differences in cognitive flexibility, based on comparisons between *GRIN2* genotypes and patterns of nicotine use.

Disclosures: E. Clarke: None. **E. Holliday:** None. **C. Parker:** None. **E. Pogue:** None.

Poster

PSTR282: Developmental, Social, and Toxic Effects of Addictive Drugs

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR282.20/II30

Topic: A.06. Developmental Disorders

Title: Maternal Nicotine Vaping Exacerbates Intestinal Injury, Neuroinflammation, and Neurobehavioral Deficits in a Mouse Model of Necrotizing Enterocolitis.

Authors: *S. WILLIAMS-MCLEOD[1], J. YOUNG[1], A. FAGUN[2], D. SCHEESE[3], T. PRINDLE[1], R. PARIKH[1], C. SODHI[1], W. FULTON[1], D. HACKAM[1], C. TRAGESSER[4]; [1]The Johns Hopkins Sch. of Med., Baltimore, MD; [2]Albion Col., Albion, MI; [3]Virginia Commonwealth Univ., Henrico, VA; [4]Richmond, VA.

Abstract: Maternal nicotine e-cigarette use during pregnancy can have detrimental effects on fetal growth and development, potentially through disruption of innate immunity by nicotine and other toxic vapor constituents. Necrotizing enterocolitis (NEC) is a severe gastrointestinal disease characterized by intestinal inflammation and tissue damage and remains a leading cause of death for premature infants. Given that infants exposed to maternal nicotine vape use during pregnancy may be at an increased risk for NEC, we hypothesized that maternal exposure to nicotine e-cigarette vapor would induce neonatal innate immune activation and exacerbate NEC severity. Using a murine model, we found that offspring exposed to nicotine vapor in utero exhibited altered placental immunity, decreased placental growth, and reduced birth weight which persisted through the first postnatal week. Combined prenatal vaping and NEC exposure worsened intestinal injury via increased oxidative stress and gut microbiome dysbiosis. Bulk

RNA sequencing of ileum and brain tissues revealed distinct transcriptomic profiles in pups exposed to maternal vaping alone or to the combination of vaping and NEC, including upregulation of complement and pro-inflammatory pathways and downregulation of genes related to epithelial barrier integrity and synaptic signaling. Importantly, prior vaping exposure exacerbated NEC-associated brain injury, as evidenced by enhanced astrocytic and microglial activation. Neurobehavioral assessments demonstrated impaired early spatial learning, increased impulsivity, and reduced grip strength, indicating both neuromuscular and cognitive deficits. Together, these findings support a model in which prenatal nicotine vaping induces immunological signaling and amplifies NEC-driven systemic inflammation, contributing to long-term intestinal and neurodevelopmental injury.

Disclosures: S. Williams-McLeod: None. **J. Young:** None. **A. Fagun:** None. **D. Scheese:** None. **T. Prindle:** None. **R. Parikh:** None. **C. Sodhi:** None. **W. Fulton:** None. **D. Hackam:** None. **C. Tragesser:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.01/II31

Topic: H.08. Drugs of Abuse and Addiction

Title: A role for Glycine Transporter-2 inhibitors in regulating accumbal dopamine levels and voluntary alcohol intake in rats

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Abstract: Alcohol Use Disorder (AUD) is a brain disorder that involves perturbations of brain dopamine (DA) systems. Previous studies have shown that alcohol interferes with inhibitory glycine receptors (GlyR) in the nucleus Accumbens (nAc), ultimately leading to increased DA release in the nAc. Also, local perfusion into the nAc and systemic treatment with the endogenous GlyR agonist glycine and with indirect GlyR agonists, *i.e.* glycine-transporter (GlyT)1-inhibitors, raise basal DA levels, attenuate alcohol-induced DA release in the nAc and reduce alcohol intake in rats. Interestingly, recent animal studies demonstrate the presence of GlyT2 in the nAc, presumably located on glycinergic axon terminals. Based on the rationale for glycine-GlyR-mediated effects on DA transmission and alcohol consummatory behavior, this study examined the role for GlyT2-inhibitors in regulating nAc glycine and DA levels and voluntary alcohol intake in rats. Effects on nAc DA and glycine levels, alcohol intake and the alcohol deprivation effect (ADE) were examined in male Wistar rats following systemic

treatment with full or partial GlyT2-inhibitors (Org-25543, Opiranserin and N-arachidonyl-glycine(NAGly)) or a combination of GlyT1 (Bitopertin) and full or partial GlyT2-inhibitors (Org-25543, NAGly), using *in vivo* microdialysis and a 2-bottle-choice (2BC) alcohol consumption model (NAGly only) with repeated cycles of alcohol deprivation. An immunohistochemistry (IHC) study was used to examine the presence of GlyT2 in the rat nAc. NAGly and Opiranserin, but not Org 25543 slightly raised nAc DA levels whereas none of the GlyT2-inhibitors altered extracellular glycine levels. Combined GlyT1- and GlyT2- inhibition did not produce significant, additive effects on extracellular DA or glycine levels. In the 2BC-model, NAGly abolished the alcohol deprivation effect. Finally, the IHC study confirmed the presence of GlyT2-expressing axonal fibers in the nAc. The reduction in alcohol intake following treatment with a partial GlyT2-inhibitor (NAGly) could be explained by its tendency to slightly elevate nAc DA levels, in line with the previously established and more pronounced effects of GlyT1-inhibition. The present findings do not unequivocally support an accumbal, intrasynaptic GlyR-mediated mechanism responsible for alterations in DA output and/or alcohol intake following GlyT2-blockade, since extracellular glycine levels measured by *in vivo* microdialysis were not altered and as effects on DA output were small. Further studies that delineate these relationships and the relevance of GlyT2 as a pharmacological target for the treatment of AUD are warranted.

Disclosures: Y. Olsson: None. **K. Danielsson:** None. **A. Domi:** None. **M. Ericson:** None. **B.E. Soderpalm:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.02/II32

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant AA031324
NIH Grant AA028352

Title: Ethanol sensitivity and tolerance: relationship to sleep in Drosophila

Authors: *V. SANCHEZ[1], L. GARCIA[2], F. W. WOLF[3];
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Abstract: Reciprocal interactions between ethanol intoxication and sleep are evident in humans and Drosophila. Investigating early ethanol adaptations can reveal neural mechanisms driving Alcohol Use Disorder (AUD). Tolerance, an early adaptation, is the acquired resistance to the pharmacological effects of ethanol. Drosophila develops rapid ethanol tolerance that is measured soon after the first binge-like ethanol dose is metabolized. I am investigating the sleep-ethanol

relationship at the single neuron level in Drosophila using the sleep promoting Dorsal Neuron 1 anterior (DN1a) neurons. The DN1a neurons are a single pair of circadian clock neurons that adjust sleep timing and depth in response to temperature and light cues. Critically, the DN1a neurons require synaptic activity and glutamatergic signaling to promote rapid ethanol tolerance, linking sleep and ethanol tolerance to the same identified neurons. We asked whether DN1a neurons promote ethanol tolerance via established temperature and sleep circuits. To test this, we combined RNAi knockdown with an ethanol sedation assay to map the DN1a tolerance circuit. Our preliminary results show the DN1a neurons do not receive input signaling from established temperature (GABA) and sleep (insulin and Pigment Disbursing Factor) neurons for promoting rapid tolerance, nor do they require a functioning clock. However, we found the DN1a neurons require the neuropeptide CCHamide-1 (CCHa1) for flies to develop tolerance. The DN1a neurons are the only clock neurons that release CCHa1, where the neuropeptide regulates the onset of evening behaviors and is responsible for the bimodal locomotor activity pattern and rhythmic activity in flies. Thus, the role of ethanol in the DN1a is decoupled from circadian clock and temperature inputs to sleep but engages a neuropeptidergic pathway that impacts sleep, providing a specific link between alcohol and sleep. Future work includes investigating neurons downstream of the DN1as, such as the DN3 Dorsal Neurons. Examining how alcohol alters signaling within the DN1a circuit will be a critical step toward mechanistically understanding the alcohol-sleep relationship.

Disclosures: V. Sanchez: None. **L. Garcia:** None. **F.W. Wolf:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.03/JJ1

Topic: H.08. Drugs of Abuse and Addiction

Support: The Homer Lindsey Bruce & Fred Murphy Jones Endowed Fellowships

Title: Genetic Dissection of Alcohol-Induced Social Behavior in C. elegans

Authors: *Y. WANG[1], K. ALI TRIBALDOS[2], J. T. PIERCE[3];
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Abstract: Alcohol use disorder (AUD) involves persistent alcohol use despite harmful consequences, and using alcohol as a social lubricant is a major risk factor for developing the disorder. Yet the neural and genetic mechanisms linking alcohol to social behavior remain unclear. Using C. elegans, we examined conserved pathways that may mediate alcohol-induced social effects. Prior work identified the BK channel as a key target of ethanol intoxication, dopaminergic signaling as a mediator of disinhibition, and Williams syndrome-related genes as promoters of social behavior in worms. Conserved stress pathways analogous to mammalian

NPY and CRF signaling also regulate anxiety-like behaviors. We found that alcohol had dose-dependent effects: depressive ethanol levels increased social interactions, whereas stimulatory levels decreased them. The decrease in social behavior did not require the BK channel, indicating a mechanism distinct from canonical intoxication. Impaired dopamine signaling increased social interaction frequency and duration, while activation of a CRF-like stress pathway amplified the social-reducing effect of stimulatory alcohol. Together, these results suggest that alcohol modulates social behavior through conserved dopaminergic and stress-related pathways. Completion of this study may reveal insights into how these key conserved pathways impinge on how alcohol modulates social behavior, with implications for not only AUD, but also social anxiety, and atypical sociality associated with autism spectrum disorder and Williams syndrome.

Disclosures: Y. Wang: None. **K. Ali Tribaldos:** None. **J.T. Pierce:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.04/JJ2

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000635 (Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section; PI: LL), jointly supported by the NIDA Intramural Research Program (IRP) and the NIAAA Division of Intramural Clinical and Biological Research (DICBR)

Title: Investigating the Association Between Peripheral Immune Markers and Alcohol Craving

Authors: *J. TYRRELL[1], R. E. TYLER[1], L. LEGGIO[2];
[1]Clin. Psychoneuroendocrinology and Neuropsychopharm. Section, Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [2]Clin. Psychoneuroendocrinology and Neuropsychopharm. Section, NIH, Baltimore, MD

Abstract: Introduction: Cue Reactivity (CR) is a measure of cravings that results from real-time exposure to external cues. Cue Exposure (CE) procedures are assessments used to elicit craving, comparing changes in CR based on different cues. This makes it a valuable assessment in studies investigating alcohol use disorder (AUD). However, some people with AUD do not react to CE assessments, suggesting that CR may represent a clinically relevant endophenotype. Recent research has shown a strong relationship between neuroinflammation and AUD. This was an exploratory analysis into potential immune markers that could guide insight into potential mechanisms behind CR-related measures.
Methods: The analysis included participants from a total of 5 clinical studies which conducted CE and measured immune markers from blood samples. CR was measured using the Alcohol Urge Questionnaire (AUQ), a self-report assessment of momentary alcohol cravings. Immune markers (IL-6, IL-8, TNF-α, CCL2, IL-10, IL-18, IL-1ra) from blood samples were measured

prior to CE. Four separate definitions of cue-reactivity were used to classify participants into cue-reactors (CR+) vs. cue non-reactors (CR-). Spearman and Spearman-like correlations were used to assess the relationship between immune markers and continuous outcomes, such as average trial AUQ scores, percent increase in AUQ, and raw difference in AUQ. Two covariate models were used to correct behavioral and/or demographic characteristics. False Discovery Rate (FDR) correction was applied to account for multiple analyses.
Results: IL-18, IL-6, and TNF-α demonstrated significant correlations with CR+ status in the covariate corrected models. IL-18 showed a positive correlation with average alcohol trial AUQ scores. No findings remained significant after FDR correction.
Conclusion: This exploratory analysis found nominally significant correlations between IL-18, IL-6, and TNF- α with the odds of being classified as a cue-reactor. This suggests that CR status may be associated with a pro-inflammatory state. These findings don't show or suggest causality; rather, they are hypothesis generating aimed at guiding further research.

Disclosures: J. Tyrrell: None. **R.E. Tyler:** None. **L. Leggio:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.05/JJ3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant AA027660

Title: ALCOHOL WITHDRAWAL SEIZURE SUSCEPTIBILITY IS ASSOCIATED WITH A REMODELING OF MEK/ERK SIGNALING IN RAT INFERIOR COLLICULUS NEURONS

Authors: G. SILVA-CARDOSO[1], A. ADEYEMI[1], *P. N'GOUEMO[2];
[1]Physiol. and Biophysics, [2]Howard Univ. Col. of Med., Washington, DC

Abstract: Background: Alcohol withdrawal seizures (AWSs) are a major complication of alcohol use disorder (AUD). Previous studies have demonstrated that elevated intracellular Ca^{2+} levels in the inferior colliculus (IC) contribute to AWS susceptibility, suggesting that downstream intracellular signaling pathways may participate in seizure generation. Among these pathways, MEK/ERK signaling is highly sensitive to neuronal hyperexcitability and alcohol exposure; however, its contribution to AWS pathophysiology remains poorly understood.
Methods: Adult male and female Sprague-Dawley rats were subjected to chronic ethanol intoxication followed by a withdrawal period. Specifically, animals received ethanol (5 g/kg, 30% v/v) or vehicle every 8 h for 4 consecutive days. IC tissues were collected at three time points: 3 h (pre-seizure susceptibility), 24 h (peak AWS susceptibility), and 48 h (resolution phase) after withdrawal. Total MEK1/2 and ERK1/2, and phosphorylated MEK (pMEK1/2) and ERK (pERK1/2) proteins were quantified by Western blotting and normalized to GAPDH. In a separate cohort, rats undergoing alcohol withdrawal were assessed for acoustically evoked

seizures, and those that exhibited seizures were administered a single dose (50 mg/kg, ip) of the MEK/ERK inhibitor SL327 and subsequently reevaluated for seizure susceptibility. Results: Ethanol withdrawal induced significant time- and sex-dependent alterations in MEK/ERK signaling within the IC. Male rats displayed transient increases in MEK and pMEK at 24 h withdrawal, corresponding to peak AWS susceptibility. In contrast, female rats exhibited increases in MEK levels at the 48 h withdrawal time point. ERK1/2 and pERK1/2 protein levels remained relatively stable across various withdrawal time points. The pMEK/MEK ratio increased significantly in females but decreased in males at peak AWS susceptibility. In contrast, the ratio pERK/ERK increased in both males and females at the same withdrawal time point. Notably, acute pharmacological inhibition of MEK/ERK signaling markedly suppressed acoustically evoked AWSs in both male and female rats. Conclusions: These findings indicate that alcohol withdrawal activates sex-specific, phosphorylation-dependent MEK/ERK signaling pathways, leading to increased IC hyperexcitability and seizure generation. Females exhibited canonical MEK-dependent ERK activation, whereas males exhibited altered MEK regulation or alternative ERK activation. Thus, the MEK/ERK pathway is proposed as a potential target for managing AWSs.

Disclosures: G. Silva-Cardoso: None. **A. Adeyemi:** None. **P. N'Gouemo:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.06/JJ4

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000635

Title: Investigating adaptations to the choroid plexus in alcohol use disorder

Authors: *N. GIRISH[1], R. E. TYLER[1], L. LEGGIO[2];
[1]Natl. Inst. on Drug Abuse (NIDA), Baltimore, MD; [2]NIH, Baltimore, MD

Abstract: Alcohol use disorder (AUD) is a chronic, relapsing disease with high morbidity and mortality. Alcohol-related organ damage is a serious consequence of AUD and in fact alcohol impacts nearly every system of the body. Furthermore, brain-periphery communications are of particular interest in understanding the disorder and developing novel treatment approaches. The Choroid Plexus (CP) is a layer of epithelial cells that lines the brain ventricles and tightly regulates access into the brain and the production of cerebrospinal fluid. While this region has been implicated in the inflammatory response to alcohol, the CP has been largely understudied in the context of alcohol and AUD. As such, we quantified the volume of the CP using structural MRI and peripheral immune markers in people with AUD compared to case-matched healthy controls (HC). The CP volume has been shown to be closely correlated with systemic and CNS inflammation, which is associated with smaller whole brain size and larger volume of ventricles.

We found that the CP volume was larger in AUD compared to HC and that the volume positively correlated with elevated peripheral levels of interleukin 8 (IL-8), IL-6, and tumor necrosis factor α (TNF-α). This could reflect inflammation of the CP as a result of alcohol-induced peripheral immune adaptations. To better understand the biological effects of AUD on the CP, we then acquired CP post-mortem brain samples from people with AUD and HC. RNA sequencing and protein expression, with a focus on immune markers, is currently underway.

Disclosures: N. Girish: None. **R.E. Tyler:** None. **L. Leggio:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.07/JJ5

Topic: H.08. Drugs of Abuse and Addiction

Support: R01-AA028782
P60-AA011605
T32-AA007573

Title: Arc and TARPy8 gene expression are exclusively upregulated in the Nucleus Accumbens of EtOH-exposed mice following cue-induced reinstatement of EtOH-seeking behavior

Authors: *C. MODRAK[1], E. SHANNON[3], S. P. FACCIDOMO[2], C. W. HODGE[4];
[2]Bowles Ctr. Alcohol Studies, [1]Univ. of North Carolina - Chapel Hill, Chapel Hill, NC; [3]UNC Sch. of Med., Chapel Hill, NC; [4]Psychiatry, Univ. North Carolina Chapel Hill, Chapel Hill, NC

Abstract: Alcohol use disorder (AUD) is a chronically relapsing disorder wherein exposure to alcohol-associated cues can trigger relapse during abstinence. Elevated AMPAR signaling throughout limbic regions are implicated in alcohol-seeking behavior, alcohol cue salience and plasticity. Such effects appear to be mediated by transmembrane AMPAR regulatory proteins (TARPs) and Arc, an immediate early gene that regulates excitatory plasticity. Despite this, whether Arc is implicated in reinstatement to alcohol-paired cues by interacting with AMPAR signaling mechanisms remains to be fully elucidated. Here, we investigated changes in genes encoding for GluA1 plasticity and transport throughout reward regions such as the amygdala, prefrontal cortex, and nucleus accumbens in mice following operant self-administration and reinstatement. Twenty female C57BL/6J mice were trained to self-administer sweetened alcohol (9% ethanol/2% sucrose) or sucrose (2%) in operant chambers for 40 days. After baseline self-administration, all mice underwent extinction procedures in which cues previously paired with the infusion of the reinforcer and the reinforcer itself were no longer present. Following successful completion of extinction training, mice were subjected to a reinstatement test one day later, in which the alcohol-paired cues were again present upon pressing, but no alcohol was delivered. Immediately after completion of reinstatement testing, all mice were sacrificed and tissue was extracted for RT-PCR. We found that both EtOH- and sucrose-exposed were

behaviorally-matched during all facets of behavioral testing, with both groups reinstating to reinforcer-paired cues when compared to the last day of extinction training. Further, Arc and TARP mRNA expression was increased after reinstatement, with regional specificity to the nucleus accumbens. This suggests that Arc and TARP may interact to regulate AMPAR synapses during heightened alcohol cue salience and seeking, and in a regionally-specific manner. Future work will test the necessity of Arc in reinstatement and identify if unique Arc ensembles encode for alcohol-seeking.

Disclosures: C. Modrak: None. **E. Shannon:** None. **S.P. Faccidomo:** None. **C.W. Hodge:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.08/JJ6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01AA030577
NIH T32AA007565

Title: Neuroimmune regulation of mesolimbic dopamine by G-CSF is altered by chronic ethanol exposure

Authors: *J. WEBB[1], R. CAMPBELL[2], C. SEITER[2], H. A. WADSWORTH[3], S. C. STEFFENSEN[4], E. S. CALIPARI[5], D. D. KIRALY[6], J. T. YORGASON[7];
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Abstract: Alcohol use disorder (AUD) is associated with neuroadaptive changes in mesolimbic dopamine (DA) signaling that contribute to reinforcement, dependence, and relapse. Mounting evidence indicates that ethanol engages immune signaling pathways; however, the neuroimmune factors that modulate DA transmission during chronic alcohol exposure remain poorly understood. Granulocyte colony-stimulating factor (G-CSF) is a cytokine implicated in reward-related behaviors and DA release, but its circuit-level actions in the context of ethanol dependence have not been explored. This study examined how G-CSF modulates mesolimbic DA signaling and neuroimmune function following chronic intermittent ethanol (CIE) exposure in mice. Using fast-scan cyclic voltammetry and calcium imaging in nucleus accumbens (NAc) slices, we found that G-CSF significantly enhanced DA terminal activity. This enhancement was accompanied by increased calcium signaling in putative ventral tegmental area (VTA) DA terminals and was abolished by nicotinic acetylcholine receptor (nAChR) blockade, indicating that G-CSF enhances DA release indirectly through cholinergic mechanisms. Consistent with

this, G-CSF receptor expression was observed in NAc cholinergic interneurons (CINs) as well as in VTA DA and GABA neurons, but no major differences were seen in tonic firing activity of these neurons. Chronic ethanol exposure produced sex-dependent adaptations, with G-CSF-induced DA signaling enhanced in females and attenuated in males following CIE. Together, these results identify G-CSF as a key neuroimmune modulator of mesolimbic dopamine signaling in the context of chronic ethanol exposure.

Disclosures: J. Webb: None. **R. Campbell:** None. **C. Seiter:** None. **H.A. Wadsworth:** None. **S.C. Steffensen:** None. **E.S. Calipari:** None. **D.D. Kiraly:** None. **J.T. Yorgason:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.09/JJ7

Topic: H.08. Drugs of Abuse and Addiction

Support: R00AA0285777

Title: Metabolic-Epigenetic Regulation of Voluntary Alcohol Drinking in Mice

Authors: *A. YADAV[1], A. MUKHERJEE[4,2], K. DODSON[7], F. DE LUNA VITORINO[5], J. A. CUCINELLO-RAGLAND[3], J. MORON-CONCEPCION[8], B. GARCIA[2], G. EGERVARI[6]; [1]Washington Univ. in St. Louis, Saint louis, MO; [2]Washington Univ. in St. Louis, Saint Louis, MO; [3]Washington Univ. in St. Louis, St. Louis, MO, ; [4]Washington Univ. Sch. of Med., St Louis, MO; [5]Washington Univ. Sch. of Med., Saint Louis, MO; [6]Washington Univ. Sch. of Med., St. Louis, MO; [7]Univ. of Pennsylvania, Philadelphia, PA; [8]Washington Univ., Saint Louis, MO.

Abstract: Epigenetic regulation, particularly histone acetylation, plays a central role in alcohol use disorder (AUD) and is strongly shaped by metabolic pathways that supply substrates for epigenetic enzymes. The alcohol-derived metabolite acetate has a particularly strong effect on the brain epigenome. We previously demonstrated that alcohol-derived acetate is directly deposited onto histones in the brain in an ACSS2 (Acetyl-CoA synthetase 2) -dependent manner and is required for alcohol-induced gene expression changes. Acetate-induced transcriptional alterations in turn influence hippocampus-dependent associative learning and alcohol consumption. However, most prior studies were limited to passive ethanol exposure, leaving the role of this pathway in voluntary alcohol intake largely unresolved. Here, we aimed to investigate the effect of ACSS2 inhibition on alcohol drinking and simultaneously identify the epigenetic changes that accompany alcohol consumption in AUD-relevant brain regions. Interestingly, we found reduced ethanol intake in mice lacking ACSS2, in a sex-specific manner. Additionally, using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), we observed changes in specific epigenetic signatures, particularly histone acetylation and histone methylation, which may underlie the effects of ACSS2 inhibition on voluntary alcohol

drinking. Overall, our work elucidates epigenetic pathways through which inhibition of the metabolic enzyme ACSS2 alters voluntary alcohol drinking and identifies novel molecular targets for therapeutic interventions in AUD.

Disclosures: A. Yadav: None. **A. Mukherjee:** None. **K. Dodson:** None. **F. de Luna Vitorino:** None. **J.A. Cucinello-Ragland:** None. **J. Moron-Concepcion:** None. **B. Garcia:** None. **G. Egervari:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.10/JJ8

Topic: H.08. Drugs of Abuse and Addiction

Title: Sex-Dependent Transcriptional Responses to Alcohol Exposure in the Mouse Parietal Cortex

Authors: *C. M. VELA[1], V. AGARWAL[2], J. WAGNER[3], J. JUNG[1], D. ROSOFF[1], T. PERLSTEIN[1], L. F. VENDRUSCOLO[4], F. W. LOHOFF[1];
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Abstract: Purpose
Chronic alcohol exposure is associated with widespread structural and functional alterations across the cerebral cortex. Emerging evidence indicates that alcohol-related brain effects differ between males and females; however, the biological mechanisms underlying sex-dependent transcriptional and neural responses to alcohol, particularly within the parietal cortex, remain poorly understood.
Methods
A total of 40 C57Bl/6J mice (20 males, 20 females) were obtained from the National Institute on Aging (NIA) colony. Young mice were 4 months old (approximately 25-30 years in humans), and aged mice were 24-26 months old (equivalent to >70 years in humans). Two age and sex groups were included: young males (n = 10) and young females (n = 10); aged males (n = 10) and aged females (n = 10). Alcohol exposure was administered using the Drinking-in-the-Dark model of binge drinking for 10 weeks. Brain transcriptional responses to alcohol were assessed by bulk mRNA sequencing from the prefrontal cortex. Differential gene expression (DGE) analyses were performed separately in males and females after adjustment for age group using DESeq2. Genes were considered differentially expressed if they had False Discovery Rate (FDR) $p < 0.05$. Further, the integrative analysis was conducted to identify sex-dependent DGE by ethanol.
Results
We found that sex affected alcohol-induced differential gene expression (DGE), but age group

did not. A preliminary analysis showed alcohol-induced expression changes in *Arc, Ier5, Bok, Dnajb5, Adra1d,* and *Arhgef25* genes in male and female mice, after adjusting for age. Collectively, these genes govern synaptic plasticity, stress responses, and neuromodulatory signaling. Further, the sex-specific genes, which exclusively alter the gene expression in females, are *Ppp1r16b, Xdh, Slc29a3,* and *Mir99ahg*, following alcohol exposure and age adjustment. These female-specific genes are associated with metabolic and regulatory pathways in response to alcohol.

Conclusion

These findings demonstrate that alcohol exposure elicits both shared and sex-specific transcriptional responses in the mouse parietal cortex. Although common alcohol-responsive genes reflect alterations in synaptic plasticity, stress regulation, and neuromodulatory signaling in both sexes, females uniquely engage additional metabolic and regulatory pathways following alcohol exposure.

Disclosures: C.M. Vela: None. **V. Agarwal:** None. **J. Wagner:** None. **J. Jung:** None. **D. Rosoff:** None. **T. Perlstein:** None. **L.F. Vendruscolo:** None. **F.W. Lohoff:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.11/JJ9

Topic: H.08. Drugs of Abuse and Addiction

Support: R01AA030577

Title: Acetaldehyde and bile acid effects on accumbal circuitry and neuroimmune interactions

Authors: *S. SHARMA[1], I. ROQUE[2], J. T. YORGASON[1];
[1]Translational Neurosci., Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [2]Brigham Young Univ., Provo, UT

Abstract: Alcohol Use Disorder (AUD) is marked by the inability to curb alcohol use despite adverse negative effects. It's known that the reinforcing effects of alcohol require mesolimbic dopamine (DA) activity. However, it's *in vivo* effects on this system are not well understood and *in vitro* studies require supraphysiological ethanol concentrations to show any effects. Peripheral organs, including the liver, represent a major target for ethanol that may contribute to *in vivo* effects through multi-organ signaling. The liver is involved in ethanol metabolism, producing the metabolite acetaldehyde and promoting bile acid (BA) secretion. Acetaldehyde and BA effects on mesolimbic dopamine (DA) circuitry are explored in the present studies, particularly exploring their effects on nucleus accumbens (NAc) cholinergic interneuron (CIN) activity, evoked DA release, and microglia morphology and motility. Cell-attached patch-clamp recordings were used to assess CIN firing, fast-scan cyclic voltammetry (FSCV) was used to measure NAc DA release, and 2-photon microscopy for microglia motility. Mouse NAc brain

slices were exposed to acetaldehyde or the BAs cholic and deoxycholic acid. No significant effects were observed with acetaldehyde (1-100 μM), suggesting a minimal role of this metabolite on NAc circuitry. A concentration dependent effect with BAs was seen where low BA concentrations (1-10 μM) increased CIN firing and DA release, whereas higher concentrations (100 μM-10 mM) suppressed both CIN firing and DA release. The low concentration effects on CIN firing were mediated through TGR5 receptors, as application of the TGR5 antagonist SBI-115 blocked the excitatory, but not inhibitory, responses. These findings highlight a dose-dependent, TGR5-dependent modulation of reward circuitry by BAs. Future experiments will test if chronic ethanol alters BA related electrophysiological responses. Overall, our results identify a novel gut-liver-brain signaling axis, offering new insights into the peripheral regulation of reward processing.

Disclosures: S. Sharma: None. **I. Roque:** None. **J.T. Yorgason:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.12/JJ10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA R01 AA031463

Title: Exploring Binge-like Alcohol Drinking in Four Core Genotypes Mice

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Abstract: Alcohol Use Disorder (AUD) is a prevalent public health issue in the United States. While AUD significantly affects both men and women, data from clinical populations highlight significant sex differences in the prevalence of the disorder: men maintain higher rates of general use and alcohol use disorder (AUD), while women exhibit vulnerabilities to related health issues and progress to AUD at faster rates. Within rodent models, females typically consume more ethanol (EtOH) than males. In the Four Core Genotypes (FCG) mouse model, the Sry gene, which directs the development of testes, is translocated from the Y chromosome onto an autosome. This model allows for exploration of the individual contributions of gonads and sex chromosome complement on EtOH consumption and aversion-resistant drinking.Previous studies from our laboratory using a two-bottle choice drinking in the dark (DID) paradigm, an established model of binge drinking that promotes escalation of ethanol intake, revealed influences of sex chromosome complement on binge intake and aversion-resistant drinking following the addition of quinine to ethanol in FCG mice. Here, we investigated whether surgical removal of the gonads alters these effects. FCG mice received gonadectomy or sham surgeries and consumed 15% ethanol in a modified DID procedure for 3 weeks. Quinine was then added to the ethanol solution in escalating concentrations to assess aversion-resistance. Consistent with

previous results, sex chromosome complement did not influence ethanol intake in female mice, regardless of surgical status. Previously observed effects on aversion-resistance were not replicated. In males, gonadectomized XY (but not XX) mice exhibited increased ethanol consumption, suggesting an interaction between sex hormones and sex chromosome complement on binge drinking. Ongoing studies are assessing whether these results apply to a standard DID procedure with a single bottle of 20% ethanol.These findings suggest that gonadal hormones and sex chromosome complement interact to produce sex-specific patterns of ethanol consumption and aversion-resistant drinking.

Disclosures: L.G. O'Lalde: None. **R.A. Zegarelli:** None. **A.K. Radke:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.13/JJ11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant AA028957
NIH Grant AA027096

Title: 10-Butyl Ether Minocycline (BEM) reduces ethanol consumption in mice via cell type - specific molecular signaling.

Authors: *P. S. ANTWI-ADJEI[1,2], P. PANTHAGANI[3], S. SHANMUGAM[2,1], J. D. CARDENAS TORO[1,2], S. E. BERGESON[1], I. PONOMAREV[2,1];
[2]Pharmacol. and Neurosci., [1]Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [3]Dept. of Physiol., LSUHSC, New Orleans, LA

Abstract: Background: Alcohol use disorder (AUD) is associated with neuroinflammation, partly driven by ethanol-induced activation of toll-like receptor 3 (TLR3). Activation of TLR3 with polyinosinic:polycytidylic acid (Poly(I:C)) increases alcohol consumption in preclinical models, although the underlying neuroimmune mechanisms remain unclear. 10-Butyl Ether Minocycline (BEM) is a non-antimicrobial immunomodulator that reduces excessive alcohol intake and preference, potentially through inhibition of microglial and neuroinflammatory pathways. This study examined whether BEM reverses TLR3-driven increases in alcohol consumption and associated molecular changes. Methods: Male and female C57BL/6J mice underwent chronic TLR3 activation with Poly(I:C) (2 mg/kg, i.p.) during a two-bottle choice every-other-day ethanol drinking paradigm. After stable escalation of intake, mice received BEM (60 mg/kg, i.p.) or vehicle before alcohol access for four drinking sessions. Ethanol consumption was measured at 6 and 24 h, and prefrontal cortex (PFC) tissue was collected 6 h after the final treatment for RNA sequencing. In a separate study, escalating BEM doses (65-85 mg/kg, i.p.) were tested for tolerance development.Results: Repeated TLR3 activation increased ethanol consumption and preference in both sexes. BEM significantly reduced ethanol intake at 6 h in

saline- and Poly(I:C)-treated mice, with weaker effects at 24 h. Escalating BEM doses produced robust acute suppression of alcohol intake but failed to maintain long-term efficacy in Poly(I:C)-treated mice. Repeated administration reduced BEM effectiveness, suggesting tolerance. Transcriptomic analyses showed that Poly(I:C) increased pro-inflammatory and endothelial-associated gene expression in the PFC of both sexes, which was attenuated by BEM. BEM also reduced microglial-, endothelial-, and pericyte-associated gene expression in alcohol-exposed saline- and Poly(I:C)-treated males, but not saline-treated females. In addition, BEM downregulated Poly(I:C)-induced immune pathways implicated in alcohol drinking behavior.Conclusions: BEM suppressed alcohol intake and reversed TLR3-mediated neuroimmune inflammation, identifying microglial and endothelial signaling as important regulators of alcohol consumption. However, tolerance with repeated dosing suggests that alternative formulations or dosing strategies may be needed to achieve sustained therapeutic efficacy.

Disclosures: P.S. Antwi-Adjei: None. **P. Panthagani:** None. **S. Shanmugam:** None. **J.D. Cardenas Toro:** None. **S.E. Bergeson:** None. **I. Ponomarev:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.14/JJ12

Topic: H.08. Drugs of Abuse and Addiction

Support: R00 AA029454

Title: Bidirectional relationship between GLT-1 and ethanol as mediated by the gut

Authors: *C. J. JOHNSTON[1], S. L. THOMPSON[2];
[1]Kahlert Inst. for Addiction Med., Univ. of Maryland, Baltimore, MD; [2]Psychiatry, Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Ethanol is among the most used drugs globally and is responsible for over 4% of all deaths. Chronic use leads to increased immune signaling and a hyperglutamatergic state in the brain, which is thought to underlie aspects of addiction and cognitive deficits. One prominent cause of this state is the broad reduction of glutamate transporter 1 (GLT-1) expression. Preliminary data showed that supplementation with the prebiotic galactooligosaccharides (GOS) can prevent this downregulation, as well as modify immune signaling. This suggests that the gut microbiome is involved in mediating ethanol's effects on GLT-1 through immune signaling which is likely dependent on Tumor Necrosis Factor (TNF). We hypothesize this prevention is mediated by the protective effects of GOS on the intestinal barrier. We first sought to determine how acute GLT-1 activation may alter ethanol drinking.
We administered a GLT-1 positive allosteric agonist (NA-014, 60 mg/kg) to male and female C57BL/6J mice after 3 weeks of ethanol administration in a drinking in the dark paradigm. This

administration did not affect ethanol consumption, suggesting that either GLT-1 activity does not acutely modify ethanol consumption, or the history of exposure reduced GLT-1 expression to a level where acute activation of remaining receptors was ineffective. As such, we next sought to determine what time course and dose of ethanol is sufficient to reduce GLT-1 expression and where in this time course GOS protects against these changes.
To test these questions, male and female C57BL/6J mice were administered either vehicle, a low (1.5 g/kg), or a moderate (3 g/kg) dose of ethanol via oral gavage either once or for five consecutive daily doses for 1-3 weeks. These mice were on a normal or GOS-supplemented diet for three weeks prior to the first ethanol administration and then throughout exposure. Mice were euthanized one hour after their final ethanol administration, and serum, brain, liver, spleen, and cecum contents were collected and fresh frozen. Blood ethanol content (BEC) was measured on an AM1 Analox and TNF levels in liver were measured via ELISA. ANOVAs were used for statistics with an alpha level of 0.05.
BEC revealed that, as expected, a higher ethanol dose led to higher BEC ($p<.001$), and more ethanol administrations exacerbated this effect ($p=.02$). TNF liver levels revealed an interaction between sex, ethanol dose, and GOS treatment ($p=.001$), which suggested a sex- and ethanol dose-dependent protective effect of GOS. GLT-1 expression was also assessed by western blot. These results suggest a role for prebiotics in the effects of ethanol and GLT-1 activation in ethanol drinking.

Disclosures: C.J. Johnston: None. **S.L. Thompson:** None.

Poster

PSTR283: Molecular, Neurochemical, and Neuroimmune Mechanisms of Alcohol

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR283.15/JJ13

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000635

Title: Investigating the effects of environmental enrichment on alcohol-related outcomes.

Authors: *D. KALLAH, R. TYLER, L. LEGGIO;
Clin. Psychoneuroendocrinology and Neuropsychopharm. Section, Translational Addiction Med. Branch, Natl. Inst. on Drug Abuse Intramural Res. Program and Natl. Inst. on Alcohol Abuse and Alcoholism Div. of Intramural Clin., Baltimore, MD

Abstract: Environmental enrichment (EE) is broadly defined as an engaging, stimulating, and complex environment as opposed to environmental deprivation, a scarce and dull environment. Pre-clinical literature shows that EE results in improved cognition, learning, and memory as well as reductions in alcohol-related behaviors in rodents. Limited human studies have also shown ecologically-relevant forms of EE are associated with decreases in alcohol intake. However, there is no prospective, randomized, controlled clinical trial directly testing the effects of EE in

people with alcohol use disorder (AUD). As such, we report preliminary analysis of the first single-blind, prospective randomized clinical trial to investigate the effects of EE in people with AUD via an experimental medicine study. Non-treatment-seeking, currently drinking participants complete two counterbalanced, 5-day stages consisting of 2-hr sessions of (1) putatively enriching activities (e.g., virtual reality, video/computer games, brain training tasks, puzzles/board games, etc.) and (2) a control (CTRL) / passive condition involving mundane, low stimulation video viewing. Following the completion of the final EE and CTRL session, participants complete laboratory-based measures in a bar-like setting, including an alcohol cue-exposure experiment to assess craving, the alcohol purchase task (APT) to assess economic demand for alcohol, and an oral alcohol challenge to assess subjective effects of alcohol. Our preliminary findings indicate that EE does not impact alcohol craving, but reduces the number of hypothetical standard drinks purchased at low prices and reduces the stimulatory effects of alcohol compared to CTRL. We hypothesize that EE may exert these effects through enhanced neuronal plasticity, and therefore plan to measure peripheral concentrations of neural trophic factors, such as the brain-derived neurotrophic factor (BDNF) and the neural growth factor (NGF). Together, these results suggest that EE may reduce the hedonic value of an alcohol reward, potentially serving as a reward substitute.

Disclosures: D. Kallah: None. **R. Tyler:** None. **L. Leggio:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.01/JJ14

Topic: H.08. Drugs of Abuse and Addiction

Title: Longitudinal assessment of synaptic remodeling following chronic cocaine self-administration using PET imaging

Authors: *I. SCHOENBORN, O. SOLÍS CASTREJÓN, M. MICHAELIDES;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Cocaine and other drugs of abuse alter synaptic structure in a region and experience dependent manner. This remodeling underlies behavioral adaptations like sensitization, craving, and relapse. Traditional methods of assessing synaptic changes rely on ex-vivo histological techniques, such as electron microscopy and immunohistochemistry, which lack the capacity for longitudinal assessment in the same subject. This project aims to assess the changes in both synaptic density and function induced by chronic cocaine self-administration through comparison with a food self-administration control. We used [18F]SynVest-1 as a proxy for synaptic density via SV2A binding, and [18F]Fluorodeoxyglucose to measure metabolic brain function. We found 15 days of chronic cocaine increased [18F]SynVest-1 uptake in the nucleus accumbens and medial prefrontal cortex that persisted after 28 days of abstinence. However, increases in brain function were only present after prolonged abstinence. This indicates a

potential uncoupling between synaptic structure and brain function that changes over time. [18F]SynVest-1 is an indirect measure of synaptic density and may also reflect changes in synaptic protein expression or vesicle availability, thus we performed electron microscopy to visualize morphological changes of the synapse itself. This revealed a similar increase in axon terminal density present in the nucleus accumbens and the medial prefrontal cortex after prolonged abstinence. Together, this project demonstrates the alterations in synapse structure, function, and morphology induced by chronic cocaine self-administration, and how these change over time. Next, we aim to use spatial transcriptomics to identify potential molecular pathways underlying the observed synaptic remodeling.

Disclosures: I. Schoenborn: None. **O. Solís Castrejón:** None. **M. Michaelides:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.02/JJ15

Topic: H.08. Drugs of Abuse and Addiction

Support: DA000069
NIH / NIDA IRP

Title: Characterization of brain function and HIV expression in HIV-1 transgenic rats.

Authors: *J. L. GOMEZ, A. E. TISCHER, O. SOLÍS CASTREJÓN, M. MICHAELIDES; NIDA / IRP, Baltimore, MD

Abstract: The goal of this project was to track changes in HIV expression in the rodent brain, as well as to characterize translational brain markers of metabolic activity, dopamine neurotransmission, and synaptic density in the context of HIV and drug exposure. We utilized a non-infectious, HIV-1 transgenic (HIV-1Tg) rat model that exhibits progressive, HIV-related phenotypes as it ages. Previous research using HIV-1Tg rats have demonstrated impaired cognition, neurodegeneration, dopamine dysregulation, cardiac and ocular pathologies akin to what is seen in the human population afflicted with HIV. Thus, using positron emission tomography (PET) and radioligands previously applied to human HIV research provides translational value to the following experiments. We scanned HIV transgenic (HIV-1Tg) rats (HIV) and wild-type (WT) controls using PET with [^{18}F]FDOPA to measure dopamine activity at baseline and after exposure to a single reinforcing dose of cocaine (15 mg/kg). We found that a single dose of cocaine produced stronger increases in [^{18}F]FDOPA (i.e., dopamine activity) in the striatum of HIV rats compared to WT rats. We then performed [^{18}F]SynVesT1 PET for synaptic density in HIV and WT rats and found that HIV rats have reduced synaptic density (lower levels of SV2A) across several brain regions compared to WT controls. Finally, with autoradiography, we assessed dopamine receptor levels for D1R, D2R, and DAT in brain tissue samples from HIV and WT rats. HIV rats have significantly lower D1R in the striatum and

nucleus accumbens but significantly greater D2R in the substantia nigra. The results suggest that HIV expression in these transgenic rats is altering dopamine function. It has been reported that patients with HIV are more susceptible to the development of substance use disorders and our model will help test novel therapeutics utilizing translational and longitudinal paradigms.

Disclosures: J.L. Gomez: None. **A.E. Tischer:** None. **O. Solís Castrejón:** None. **M. Michaelides:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.03/JJ16

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R01DA014133
P01DA047233
P30DA01834
K01DA060334

Title: Synaptic neuroproteomic signatures of cocaine withdrawal across mesocorticolimbic brain regions

Authors: *G. TAN, A. GODINO, Y. YIM, E. J. NESTLER;
Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Substance use disorders (SUD) continue to be a significant public health problem in the United States, presenting a challenge for effective treatment due to their complex neurobiological mechanisms. Dysregulated signaling within reward-processing brain regions, such as prefrontal cortex (PFC), ventral hippocampus (vHipp), and dorsal striatum (dStri), plays a critical role in cue- and context-induced reinstatement and compulsive use of substance. Relative to our understanding of transcriptional responses to drugs of abuse, our knowledge about changes in the proteomic landscape of synapses is limited. Identifying these changes could reveal more effective targets for SUD treatment. In this study, we build upon previous research on cocaine-mediated proteomic adaptations by focusing on the discovery of sex- and withdrawal (WD)-dependent changes in the synaptic proteome of the PFC, vHipp, and dStri. Adult male and female C57BL/6J mice (12 weeks old) were subjected to daily cocaine (20 mg/kg) or saline (vehicle) intraperitoneal (I.P.) injections for 7 days, followed by 24 hours or 30 days of forced abstinence (withdrawal; WD). After WD, the NAc and PFC were extracted, and synaptosomes were purified and analyzed using lipid chromatography-tandem mass spectrometry (LC-MS/MS) followed by label-free quantification at the Yale/NIDA neuroproteomics core. Through this analysis, we identified multiple synapse-enriched proteins that were induced or repressed in a brain region-, sex-, and WD-time dependent manner. While most of these cocaine-regulated proteins are expressed by neurons, a significant subset is enriched in astrocytes or microglia,

consistent with the involvement of these cell types in synaptic processes. In the PFC after 24 hours of WD, male mice displayed ~2.5 times more significant proteome changes (primarily repression) than female mice. We are currently validating these findings to identify candidate synaptic proteins that directly contribute to drug-seeking behavior in a brain region-, sex-, and WD-time dependent manner. This study aims to enhance our understanding of the molecular restructuring of synapses in the reward circuitry, which ultimately influences susceptibility to relapse.

Disclosures: G. Tan: None. **A. Godino:** None. **Y. Yim:** None. **E.J. Nestler:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01DA014133
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Title: Sex- and Withdrawal-Dependent Remodeling of the Synaptic Proteome in the Nucleus Accumbens After Cocaine Exposure Reveals Ephexin1 as a Regulator of Cocaine Seeking

Authors: *Y. YIM[1], T. MARKOVIC[2], A. LABANCA[3], Z. XU[4], G. TAN[2], R. FUTAMURA[2], A. GODINO[2], V. KONDEV[2], L. HOLT[2], E. KAHN[1], T. M. GYLES[3], Y. DONG[5], E. J. NESTLER[3];
[2]Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [4]Univ. of pittsburgh, Pittsburgh, PA; [5]Dept Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Substance use disorders are characterized by persistent relapse vulnerability driven by long-lasting neuroadaptations within reward-related brain circuits, including the NAc. While transcriptional adaptations to cocaine exposure have been extensively studied, cocaine-induced remodeling of the synaptic proteome remains poorly understood. Adult male and female C57BL/6J mice received daily I.P. injections of cocaine or saline for 7 days followed by either 1 or 30 days (WD) of forced abstinence to characterize sex- and withdrawal-dependent synaptic proteomic changes. Crude synaptosomes were isolated from the NAc and analyzed using LC-MS/MS with label-free quantification at the Yale/NIDA Neuroproteomics Center. Differential expression analyses identified numerous cocaine-regulated proteins (±20% fold change, $p < 0.05$), and network analyses revealed synaptic pruning-related protein clusters across withdrawal and sex conditions. Among the differentially expressed proteins, ephexin1, a guanine nucleotide

exchange factor, emerged as a key candidate. Ephexin1 expression increased in both sexes at 1WD; however, at 30WD, ephexin1 remained elevated in males while decreasing in females. Functional relevance was assessed by manipulating ephexin1 expression in the NAc using viral-mediated overexpression (OE) and knockdown (KD) during cocaine self-administration. In male mice, ephexin1 OE reduced active lever pressing and cocaine intake, whereas females showed no significant behavioral changes after OE. Ephexin1 KD did not alter cocaine intake in either sex. Neither OE nor KD altered saccharin self-administration, suggesting specificity for cocaine-related behaviors. Mice also underwent open field, elevated plus maze, and social interaction testing. In males, ephexin1 OE increased locomotor activity and anxiety-like behavior while reducing social interaction. In females, ephexin1 KD reduced social interaction without affecting locomotion or anxiety-like behavior. Cellular mechanisms underlying these behavioral adaptations were examined using whole-cell patch-clamp recordings in Drd1- and Drd2-tdTomato mice following ephexin1 OE. Ephexin1 OE reduced neuronal activity in both D1- and D2-medium spiny neurons, indicated by reduced evoked action potentials and increased rheobase. Excitatory and inhibitory synaptic transmission were unchanged, suggesting ephexin1 alters intrinsic membrane excitability. Together, these findings reveal sex- and withdrawal-dependent remodeling of the NAc synaptic proteome after cocaine exposure and establish ephexin1 as a novel regulator of cocaine seeking and neuronal excitability.

Disclosures: Y. Yim: None. **T. Markovic:** None. **A. LaBanca:** None. **Z. Xu:** None. **G. Tan:** None. **R. Futamura:** None. **A. Godino:** None. **V. Kondev:** None. **L. Holt:** None. **E. Kahn:** None. **T.M. Gyles:** None. **Y. Dong:** None. **E.J. Nestler:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.05/JJ18

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA058958
R01DA058098
R00DA045795
R34DA061267
P30DA033934
BLICK SCHOLAR FUNDS

Title: Re-designing the function of KRAB zinc finger proteins in mouse nucleus accumbens to augment the transcriptional origins of drug use behaviors.

Authors: *A. HASSAN[1], J. PICONE[3], P. J. HAMILTON[2];
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Abstract: Chronic substance use produces molecular and behavioral adaptations that contribute to the vulnerability of developing substance use disorders (SUDs), particularly within the neurons of the nucleus accumbens (NAc). Although the mechanisms underlying SUDs have been studied, the relationship between transcriptional control of non-canonical genes, such as brain transposable elements (TEs), and SUDs remains largely unexplored. Approximately 50% of the human genome is composed of TEs, some of which replicate and reinsert into different locations in the genome. TEs are largely transcriptionally silenced to preserve genomic stability and prevent reinsertion events. TE transcriptional repression is mediated by KRAB zinc finger proteins (KZFPs) transcription factors via the transcriptional corepressor TRIM28. Our lab has created synthetic variants of TRIM28 to augment KZFP function and activate TE transcription in the brain. The $TRIM28^{WT}$ variant is identical to the endogenous transcriptionally repressive TRIM28 and the novel $TRIM28^{VPR}$ variant acts as a synthetic transcriptional activator at KZFP gene targets and TEs. We utilized these TRIM28 variants of opposite function to characterize the effect of KZFP function on drug seeking, reinforcement and gene expression by delivering TRIM28 variants to the NAc of awake and behaving mice. Our lab has previously demonstrated one KZFP, ZFP189, facilitates cocaine-related behavioral and transcriptional adaptations and led us to the hypothesis that KZFP-mediated gene regulatory control, including TEs, is causal in producing cocaine-specific gene expression and behaviors. In order to test this, we characterized the effect of TRIM28 variants in the NAc on cocaine drug-seeking behaviors using conditioned place preference to determine changes in the rewarding properties of cocaine. Secondly, we determined the effect of TRIM28 function on cocaine reinforcement by using intravenous self-administration to dose-dependently determine the change in reinforcement before and after delivery of TRIM28 variants to the NAc. Lastly, we performed a locomotor assay across TRIM28 variants using cocaine and morphine and extracted the NAc for RNAsequencing and generated differentially expressed genes and TEs relative to saline-treated mice. Our findings indicate that KZFP-mediated transcriptional control of the mouse NAc alters cocaine reward processes and reinforcement and produces sex differences among differentially expressed genes and TEs. Our studies suggest that this mechanism may contribute to the molecular processes that govern drug-taking behaviors and drug-related gene expression.

Disclosures: A. Hassan: None. **J. Picone:** None. **P.J. Hamilton:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.06/JJ19

Topic: H.08. Drugs of Abuse and Addiction

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NIH Grant F32DA055438
George E. Hewitt Foundation

Title: Investigating transcriptomic changes linking nucleus accumbens cholinergic interneuron NR4A2 function with accumbens physiology and cocaine-associated behaviors

Authors: *T. L. FETTERLY[1,3], J. E. CHILDS[5], M. R. TETZLAFF[1], G. SANDOVAL[2], E. A. KRAMAR[3], D. P. MATHEOS[3], J. DÍAZ-ALONSO[2], T. Z. BARAM[4], M. A. WOOD[3]; [2]Anat. & Neurobio., [1]Univ. of California, Irvine, Irvine, CA; [3]Neurobio. & Behavior, [4]Anatomy/Neurobiology; Pediatrics, Univ. of California Irvine, Irvine, CA; [5]Biomed. Sci., Marshall Univ., Huntington, WV

Abstract: Substance use disorder (SUD) is characterized by a lifelong risk of relapse, contributing to the complexity of treatment. This persistent vulnerability to relapse is in part driven by the formation of abnormally strong context/reward memories. Epigenetic regulation plays a major role in supporting persistent changes in cell function, that give rise to altered circuit plasticity and ultimately lead to long-lasting changes in behavior. Understanding changes in epigenetic regulation that are programmed during drug use will provide insight to identifying mechanisms underlying these strong drug-associated memories. The epigenetic regulator histone deacetylase 3 (HDAC3) has been identified as a negative regulator of gene expression that is important for long-term memory formation. Downstream, we have identified NR4A2, a transcription factor, as a key target gene of HDAC3. The Wood lab has demonstrated an important role of NR4A2 in cholinergic neurons in both the medial habenula and nucleus accumbens (NAc) in regulating cocaine-associated behaviors. Our recent work in NAc cholinergic interneurons (ChIns) utilizes a transcriptionally inactive (but endogenously expressed) dominant negative form of NR4A2 (NURR2C). We utilized ChAT-Cre mice to target our viral expression of NURR2C specifically to NAc ChIns. Reducing NR4A2 function in NAc ChIns resulted in overall decreased firing frequency of these neurons. Downstream, this resulted in both pre- and post-synaptic changes in glutamatergic signaling onto medium spiny neurons (MSNs) and an overall enhancement in field potential long-term potentiation. In addition to these physiological changes, NURR2C expression in NAc ChIns also enhances cocaine-associated behaviors using both models of conditioned place preference (CPP) and intravenous self-administration. To further investigate the mechanisms linking the expression of NURR2C to physiological and behavioral changes, we are currently utilizing the MERFISH platform to examine spatial expression of RNA. We are examining spatial transcriptomic changes induced by NURR2C expression and how this is altered by cocaine/acquisition of CPP. Overall, these results will further our understanding of NR4A2 regulation of NAc physiology, providing insights into cell-to-cell communication and mechanisms supporting drug-associated memories.

Disclosures: T.L. Fetterly: None. **J.E. Childs:** None. **M.R. Tetzlaff:** None. **G. Sandoval:** None. **E.A. Kramar:** None. **D.P. Matheos:** None. **J. Díaz-Alonso:** None. **T.Z. Baram:** None. **M.A. Wood:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01 DA047265
NSF GFRP Fellowship 2038235
Temple University CARAS Research Grant

Title: Cell-specific analysis of PICK1 expression in DRD1 medium spiny neurons of the nucleus accumbens following cocaine self-administration

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Abstract: Substance use disorder (SUD) is associated with drug-induced neuroadaptations within brain reward circuitry, including alterations in glutamatergic signaling in the nucleus accumbens (NAc). Protein interacting with C kinase 1 (PICK1), a regulator of AMPA receptor trafficking and synaptic plasticity, has recently been implicated in cocaine-induced neuroadaptations. Previous work from the Briand laboratory demonstrated that cocaine self-administration decreases PICK1 expression in the NAc; however, whether these alterations occur specifically within dopamine receptor D1 (DRD1)-expressing neurons and whether they differ by biological sex remains unclear. Because DRD1- and DRD2-expressing medium spiny neurons contribute differently to reward-related behaviors, identifying cell-specific changes in PICK1 expression may provide insight into mechanisms underlying cocaine-induced plasticity. To examine this, adult male and female drug-naïve and cocaine self-administering mice were used for RNAscope multiplex fluorescent in situ hybridization targeting PICK1 and DRD1 mRNA in the NAc. Confocal microscopy and image analysis were used to quantify PICK1 and DRD1 expression and PICK1-DRD1 colocalization within DRD1-expressing neurons. Preliminary analyses from drug-naïve mice indicate no significant baseline sex differences in PICK1 expression or localization within DRD1 neurons of the NAc. Ongoing analyses are examining whether cocaine self-administration alters PICK1 expression in a sex-dependent manner within DRD1-expressing neurons. These studies will provide insight into cell-specific glutamatergic adaptations associated with cocaine exposure and may identify sex-dependent mechanisms contributing to SUD vulnerability.

Disclosures: S. Bhanushali: None. **M.Y. Roberts:** None. **L.M. Hubbard:** None. **L.A. Briand:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Program #/Poster #: PSTR284.08/JJ21

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA049930

Title: Cell-type-specific modulation of PKA in nucleus accumbens core medium spiny neurons during incubation of cocaine craving

Authors: T. YIU, E.-K. HWANG, J. G. WESTLAKE, L. R. TEPE, ***M. E. WOLF**; Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: Persistent vulnerability to relapse is a major challenge in treating substance use disorder. In the incubation of craving model, cue-induced drug seeking in rats progressively intensifies after abstinence from cocaine self-administration (SA). Our previous work showed that cocaine incubation requires strengthening of excitatory synapses in the nucleus accumbens core (NAcc) by upregulation of calcium-permeable AMPA receptors (CP-AMPARs) in D1 medium spiny neurons (MSNs). However, although dopamine (DA) signaling in the NAcc is important for motivated behavior, its role in incubation is still not well understood. Recent work from our lab showed that DA transients during cue-induced seeking do not increase after incubation, suggesting that incubation may involve altered postsynaptic responsiveness to DA rather than increased DA release. Since DA receptors regulate downstream PKA signaling, we hypothesized that incubation is associated with changes in cell-type-specific PKA activity in NAcc MSNs. To test this, we expressed ExRai-AKAR2 in the NAcc of adult male or female D1-Cre or A2a-Cre rats to monitor PKA activity in D1-MSNs or A2a/D2-MSNs. Rats underwent extended-access cocaine SA (6 h/day × 10 days). During SA, active pokes resulted in cocaine infusion paired with a light cue, whereas inactive pokes had no consequence. Fiber photometry was performed during cue-induced seeking tests on abstinence day 1 (AD1) and AD40, during which active pokes resulted in cue presentation without infusion. Preliminary AD1 recordings showed an increase in D1-MSN PKA activity in response to active pokes, consistent with prior work showing cue-locked DA release during cocaine seeking. Surprisingly, active pokes also elicited PKA activation in D2-MSNs. This was unexpected because DA acting at Gi-coupled D2 receptors would be expected to suppress PKA, suggesting involvement of additional neuromodulatory inputs such as adenosine/A2a signaling. To test whether D1-MSN PKA contributes to incubation, we expressed PKIα in D1-Cre rats to inhibit PKA activity in D1-MSNs. In our pilot cohort, PKIα-expressing rats showed only a small increase in active pokes from AD1 to AD40 (mean = 2). Slice recordings from their D1-MSNs showed no apparent CP-AMPAR upregulation (8 cells/2 rats, rectification index = 1.08 ± 0.02). Together, these results suggest that cocaine seeking engages intracellular PKA signaling in D1- and D2-MSNs through distinct mechanisms, and that D1-MSN PKA activity may contribute to CP-AMPAR accumulation and incubated cocaine craving. Ongoing studies are testing whether prolonged abstinence alters PKA dynamics in D1- and D2-MSNs during cocaine seeking.

Disclosures: T. Yiu: None. **E. Hwang:** None. **J.G. Westlake:** None. **L.R. Tepe:** None. **M.E. Wolf:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Program #/Poster #: PSTR284.09/JJ22

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA066150

Title: Dopamine D2 Receptor Activation Dynamics Shape Signaling Bias

Authors: *M. NEWLIN, E. MATTHIESSEN, P. DONTHAMSETTI;
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Abstract: Dopamine receptors modulate complex physiological processes and are implicated in cocaine use disorder (CUD). Among them, dopamine D2 receptor (D2R) is a particularly compelling target, undergoing functional changes in response to cocaine and showing promise in preclinical models. D2R-targeting drugs have failed in clinical trials, emphasizing the need for a deeper understanding of D2R function. D2R is a G protein-coupled receptor (GPCR) that engages canonical $G_{i/o}$- and non-canonical arrestin-dependent signaling. Recent advances indicate that these signaling pathways control distinct behavioral processes, raising the possibility that they could be selectively targeted to enhance clinical efficacy and reduce adverse side effects. While GPCRs are often viewed as binary on-off switches, emerging evidence suggests that the dynamics of receptor activation strongly influence downstream signaling. Here, we combined cutting-edge pharmacology and analytical modeling to define how D2R activation dynamics shape signaling.We determined the kinetics of dopamine-dependent D2R signaling using bioluminescence resonance energy transfer (BRET)-based functional assays. We applied increasing concentrations of dopamine to cells expressing D2R and measured changes in multiple downstream endpoints (G_o, G_i, arrestin). We found that sub-saturating dopamine concentrations favor G protein signaling. This balance shifted toward arrestin following sustained receptor activation. While these studies provide a framework for understanding dopamine action, dopamine release *in vivo* fluctuates between low nanomolar baseline levels (tonic) and sub-second micromolar bursts (phasic). To mimic these dynamics, we leveraged a novel method developed by our lab called membrane-anchored photoswitch (MP) that combines a membrane-anchor protein (M) and a light-controllable agonist (P) to enable precise temporal control of D2R activation. We then combined this technology with real-time detection of receptor signaling by developing a “write-read” system wherein light is injected directly into a plate reader. Strikingly, D2R activation patterns mimicking phasic dopamine release robustly engaged G protein signaling while eliciting minimal arrestin recruitment, indicating that the temporal dynamics of D2R activation can bias signaling toward specific pathways.This study begins to elucidate the relationship between D2R activation dynamics and function *in vitro*, informing efforts to understand the mechanisms and implications of D2R signaling bias *in vivo*. More broadly, it provides a template to uncover the role of diverse neuronal GPCRs in health and disease.

Disclosures: M. Newlin: None. **E. Matthiessen:** None. **P. Donthamsetti:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 1R15DA060396
Claire E McGregor Endowed Professorship

Title: Investigating the Role of D1 Receptors in Sex Differences in Cocaine-Induced Impulsivity

Authors: S. VO, A. BAIRD, Z. KAYA, ***T. A. PAINE**;
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Abstract: Substance use disorder (SUD) continues to be a significant public health concern in the United States. Although males are more likely to use cocaine, recent reports suggest that the gender gap is narrowing. Further, females are more vulnerable than males to key phases in the trajectory of SUDs, including drug bingeing and relapse. Impulsivity is an important risk factor for the development of SUD and may contribute to the observed sex difference in patterns of drug use. Notably, we have previously observed that female rats exhibit more robust cocaine-induced impulsivity compared to male rats using a differential reinforcement of low rates of responding task (DRL). Additionally, we observed that these changes were associated with changes in dopamine D1 receptor expression in the striatum and prefrontal cortex. Because increases in dopamine function are associated with changes in impulsivity, we hypothesized that cocaine-induced changes in DRL performance were mediated by the observed sex difference in D1 receptor expression. Male and female rats were trained to respond on a DRL-10 second task; responses occurring with inter-response times (IRT) of greater than 10 sec were rewarded while responses with IRTs of less than 10 sec were not rewarded and restarted the 10-sec timer. Once rats reached stable levels of performance, the effects of SCH23390 (a D1 receptor antagonist) and SKF81297 (a D1 receptor agonist) on task performance were assessed. Additionally, the ability of SCH23390 to attenuate the effects of cocaine on DRL performance were assessed. SCH23390 dose-dependently decreased measures of impulsivity and increased task disengagement from baseline levels in both male and female rats; the latter effect was more pronounced in females. SKF81297 caused a small, but reliable increase in impulsive behavior in both sexes but impaired motor function in females and enhanced motor function in males. Administering SCH23390 prior to cocaine partially attenuated measures of cocaine-induced impulsivity in both males and females and reduced the motor activating effects of cocaine in males. Consistent with past findings, we observe that female rats exhibited more robust cocaine-induced impulsivity and more pronounced task disengagement relative to male rats. Contrary to our hypothesis, female rats were not more sensitive to the effects of D1 receptor blockade on cocaine-induced impulsivity. These data suggest that some other mechanism contributes to the observed sex difference in impulsivity.

Disclosures: S. Vo: None. **A. Baird:** None. **Z. Kaya:** None. **T.A. Paine:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.11/JJ24

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant ZIADA000069

Title: Synaptic Zn^{2+} regulation of dopaminergic transmission in the nucleus accumbens during repeated cocaine exposure

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Abstract: Synaptic Zn^{2+} is co-released with glutamate from a subset of glutamatergic neurons and acts as an endogenous modulator of dopamine neurotransmission in the striatum. Previous studies demonstrated that Zn^{2+} binds to the dopamine transporter (DAT) and enhances cocaine-induced behaviors. However, the effects of Zn^{2+} on other components of the dopaminergic system and the dynamics of Zn^{2+} signaling during repeated cocaine exposure remain poorly understood. In this study, we combined autoradiography and fiber photometry to investigate the effects of Zn^{2+} on dopaminergic signaling and to characterize adaptations in Zn^{2+} and dopamine-related activity during cocaine sensitization. Autoradiography experiments were performed in striatal tissue from saline- and cocaine-treated mice using [^{3}H]WIN-35,428, [^{3}H]SCH23390, and [^{3}H]raclopride to quantify binding to DAT, dopamine D1 receptors (D1R), and dopamine D2 receptors (D2R), respectively, in the presence or absence of physiological concentrations of Zn^{2+}. Consistent with previous findings, Zn^{2+} significantly increased [^{3}H]WIN-35,428 binding to DAT. In contrast, Zn^{2+} did not alter [^{3}H]SCH23390 binding to D1R. Zn^{2+} decreased [^{3}H]raclopride binding to D2R, suggesting that Zn^{2+} may modulate D2 receptor binding. We then performed fiber photometry recordings in the nucleus accumbens during five days of cocaine sensitization (15 mg/kg, i.p.). Repeated cocaine administration increased dopamine dynamics (GRABDA2m) compared with saline-treated animals. In contrast, synaptic Zn^{2+} dynamics (GRISZ) showed an initial decrease following cocaine administration that gradually recovered and exceeded baseline levels. A similar temporal profile was observed for cAMP dynamics (G-Flamp1) in D2 neurons. In addition, activity of dopaminergic terminals (axon-GCaMP) progressively increased across repeated cocaine exposures. These findings suggest that Zn^{2+} modulates multiple components of the dopaminergic system, including DAT and D2 receptors. In addition, repeated cocaine exposure induces changes in synaptic Zn^{2+} dynamics that occur alongside adaptations in dopamine release, dopaminergic terminal activity, and D2 neuron signaling in the nucleus accumbens. Together, these results support a role for synaptic Zn^{2+} in cocaine-induced neuroadaptations.

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Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.12/KK1

Topic: H.08. Drugs of Abuse and Addiction

Support: K01DA053434
R37DA054370

Title: cAMP and Neuroimmune Signaling in Accumbens D2 Neurons Regulate Individual Variability in Cocaine Seeking

Authors: *L. FUENTES[1], J. PARRILLA FUENTES[4], S. SHARMIN[2], T. C. JHOU[5], J. PARRILLA CARRERO[3];
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Abstract: Cocaine is a potent reinforcer, yet individual susceptibility to persistent cocaine seeking is variable. We hypothesized that this variability is attributable, at least in part, to the recruitment of protective adaptations within the nucleus accumbens medial shell D2 medium spiny neurons that serve to limit cocaine seeking. To address this, we employed a rat runway paradigm in both male and female Long-Evans rats and observed marked differences in cocaine-seeking behavior. To validate these behavioral phenotypes, we subjected animals to punishment testing. High-cocaine-seeker rats persisted in cocaine seeking despite escalating foot shock intensity, whereas low-cocaine-seeker rats exhibited a reduction in cocaine-seeking behavior under aversive conditions. Cell-type-specific fiber photometry recordings indicated that cocaine administration resulted in a suppression of D2 neuron calcium activity in high-seekers, while low-seekers exhibited either preserved or increased D2 calcium transients. In vivo cAMP photometry demonstrated that, despite similar cocaine-evoked dopamine release across groups, high-seekers exhibited reduced D2 neuron cAMP levels, consistent with canonical D2 receptor signaling. In contrast, low-seekers displayed elevated D2 cAMP levels, indicative of a noncanonical signaling state associated with resilience. Molecular analyses of medial shell tissue, including D2 neuron-specific RNA sequencing, revealed that high-cocaine-seeker rats exhibited increased Stat4 expression, whereas low-cocaine-seeker rats showed reduced Stat4 and elevated Socs5 expression, the latter encoding a negative regulator of STAT signaling. Targeted knockdown of Stat4 or overexpression of Socs5 in D2 neurons in behaving animals resulted in a reduction of cocaine-seeking behavior. These findings indicate that resilience to cocaine seeking is associated with coordinated intracellular adaptations in accumbens D2 neurons, including preserved calcium signaling, increased cAMP, upregulation of SOCS5, and downregulation of STAT4 signaling. Further investigation will be required to delineate the interaction between cAMP and neuroimmune signaling in D2 neurons and its contribution to individual variability in cocaine-seeking behavior.

Disclosures: L. Fuentes: None. **J. Parrilla Fuentes:** None. **S. Sharmin:** None. **T.C. Jhou:** None. **J. Parrilla Carrero:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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Topic: H.08. Drugs of Abuse and Addiction

Support: K01DA053434
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Title: RhoA-ROCK Signaling in Accumbens D2 Neurons Promotes Resilience to Cocaine Seeking

Authors: S. SHARMIN[1], **L. FUENTES**[2], J. PARRILLA FUENTES[4], T. C. JHOU[5], *J. PARRILLA CARRERO[3];
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Abstract: RhoA-ROCK signaling is known to regulate cytoskeletal remodeling, synaptic strength, and experience-dependent plasticity. However, the specific contribution of this pathway to individual differences in vulnerability or resilience to cocaine seeking has not been fully elucidated. We employed a rat runway model to distinguish high- and low-cocaine-seeking phenotypes in both male and female Long-Evans rats. High-seekers exhibited greater motivation for cocaine, as evidenced by increased punishment-resistant cocaine seeking relative to low-seekers. Biochemical analyses revealed that low-seekers displayed enhanced activity of the RhoA-ROCK pathway within the medial shell of the nucleus accumbens. Specifically, we observed increased levels of RhoA-GTP and elevated ROCK activity in low-seekers compared to both high-seekers and saline-treated controls. To investigate whether resilience-associated adaptations were localized to medial shell D2-expressing neurons, we conducted D2-specific RiboTag-assisted RNA sequencing. In low-seekers, we detected increased expression of Arhgef25, a guanine nucleotide exchange factor that facilitates RhoA activation, while the expression levels of RhoA, Rock1, and Rock2 remained unchanged. These findings indicate that resilience is associated with an increased capacity for RhoA activation rather than upregulation of core RhoA-ROCK pathway components. To establish causality, we performed functional manipulations: D2 neuron-specific overexpression of Arhgef25 shifted animals toward a low-seeker phenotype, whereas D2-specific expression of dominant-negative RhoA resulted in increased cocaine seeking. We next tested whether activating RhoA in medial shell D2 neurons is sufficient to suppress cocaine seeking in established high-seekers. Using an optogenetic strategy to transiently activate RhoA, we observed a reduction in cocaine seeking in high-seeker animals. This effect was abolished by administration of the ROCK inhibitor Fasudil, indicating that RhoA-mediated suppression of cocaine seeking requires ROCK-dependent signaling. Collectively, these results identify ARHGEF25-RhoA-ROCK signaling within medial shell D2 neurons as a causal molecular mechanism underlying resilience to cocaine seeking.

Disclosures: S. Sharmin: None. **L. Fuentes:** None. **J. Parrilla Fuentes:** None. **T.C. Jhou:** None. **J. Parrilla Carrero:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

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National Research Foundation of Korea RS-2024-00463082
the Korea Institute of Science and Technology 26Z9001

Title: Cell type-specific regulation of cocaine-associated behaviors and neuronal function by MeCP2 in nucleus accumbens D2 neurons

Authors: *J. BAE[1], Y.-E. HAN[1], S.-J. OH[1,2], H.-I. IM[1,2];
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Abstract: Cocaine addiction is a chronic relapsing disorder marked by persistent vulnerability to drug-associated behaviors. The nucleus accumbens (NAc) is a key hub for addiction-related plasticity, yet the cell-type-specific mechanisms contributing to cocaine-induced behavioral vulnerability remain incompletely understood. Here, we examined methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulator associated with neuronal plasticity, to determine whether cocaine alters MeCP2 in a cell-type-biased manner within the NAc and whether selective manipulation of MeCP2 in dopamine D2 receptor-expressing (D2R+) neurons is associated with changes in cocaine-related behaviors and neuronal function. Following repeated cocaine exposure and withdrawal, MeCP2 protein levels were reduced in the NAc, with a greater decrease observed in D2R+ neurons than in D1R+ neurons. To assess the functional relevance of this change, MeCP2 was bidirectionally manipulated in NAc D2R+ neurons using viral overexpression or knockdown. In behavioral assays, D2R-selective MeCP2 manipulation was associated with bidirectional changes in cocaine-related phenotypes: MeCP2 overexpression reduced behavioral sensitivity to cocaine re-exposure, whereas MeCP2 knockdown enhanced it. In conditioned place preference paradigms incorporating conditioning, extinction, and reinstatement-like testing, MeCP2 manipulation bidirectionally influenced relapse-related behavioral expression. In cocaine self-administration, D2R-targeted MeCP2 overexpression attenuated cocaine taking and seeking. Whole-cell patch-clamp recordings further indicated that MeCP2 manipulation altered the intrinsic excitability and excitatory synaptic properties of D2R+ neurons. In particular, MeCP2 overexpression was associated with normalization of cocaine-related electrophysiological alterations, including changes in spike output and excitatory synaptic

transmission. Together, these findings suggest that MeCP2 in NAc D2R+ neurons may contribute to cocaine-associated behavioral vulnerability and electrophysiological plasticity.

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Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR284.15/KK4

Topic: H.08. Drugs of Abuse and Addiction

Support: DA014133

Title: Circuit and transcriptomic mechanisms for dopamine receptor D2-expressing neurons in paraventricular nucleus of the thalamus: Role in cocaine-seeking behavior

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Abstract: Substance use disorder (SUD) is a chronic relapsing disorder characterized by persistent drug seeking triggered by drug-associated cues despite adverse consequences. The paraventricular nucleus of the thalamus (PVT) has emerged as a key node linking internal states with motivated behavior (drug-seeking). The PVT sends dense projections to canonical reward regions, including the nucleus accumbens, and is robustly activated by drug paired cues; animals exhibiting high levels of reinstatement show significantly greater FOS expression in PVT. Although posterior PVT (pPVT) activity is strongly associated with cocaine seeking, the cell-type-specific mechanisms underlying this process remain poorly understood. Dopamine receptor D2-expressing neurons in the pPVT ($pPVT^{D2+}$) represent a particularly compelling population, as enhanced D2 signaling in this region attenuates cocaine-induced locomotor sensitization. Here, we tested the hypothesis that cocaine induces persistent functional adaptations within $pPVT^{D2+}$ neurons that contribute to cocaine-seeking behavior. We found that chronic cocaine significantly increased ΔFOSB expression in $pPVT^{D2+}$ neurons, indicating sustained recruitment of this population. Furthermore, chemogenetic inhibition of $pPVT^{D2+}$ neurons attenuated cocaine conditioned place preference (CPP) and reduced cue-induced cocaine seeking following intravenous cocaine self-administration. Conversely, knockdown of D2 receptors within the pPVT enhanced cocaine-associated behaviors, supporting an inhibitory role for D2 signaling in cocaine reward and seeking. To investigate the circuit dynamics underlying these behavioral

effects, we employed wireless fiber photometry to monitor dopamine signaling and $pPVT^{D2+}$ neural activity during cocaine self-administration. Using GRABDA sensor our recordings revealed rapid within-session adaptations in pPVT dopamine signaling during cue-induced cocaine seeking, demonstrating dynamic regulation of dopamine transmission within this brain region. These findings identify $pPVT^{D2+}$ neurons as a critical regulator of cocaine seeking and establish D2 receptor signaling within the pPVT as an important modulator of cocaine-associated behaviors. Together with ongoing calcium imaging and single-nucleus RNA sequencing studies, these results provide new insight into the circuit dynamics and molecular adaptations through which $pPVT^{D2+}$ neurons contribute to cocaine-seeking vulnerability and relapse-related behaviors.

Disclosures: T. Markovic: None. **Y. Yim:** None. **G. Tan:** None. **V. Kondev:** None. **R. Futamura:** None. **G. Di Salvo:** None. **A. LaBanca:** None. **I.S. Maze:** None. **P. Roussos:** None. **E.J. Nestler:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.16/KK5

Topic: H.08. Drugs of Abuse and Addiction

Title: The parasubthalamic nucleus drives cocaine-induced compulsive behavior via serotonergic signaling

Authors: *T. KIM[1], S. LEE[2], S. CHOI[1], J. SHIN[1], J. PYO[1], J.-H. KIM[1];
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Abstract: Drug addiction manifests through diverse phenotypic expressions, and one of the core features is compulsive behavior - ‘behavioral persistence despite negative consequences’. Drug addiction is often defined as substance use disorder, characterized by continued use of drugs despite harm; thus, compulsive behavior represents the most salient pathological hallmark of addiction. Our goal is to find out the specific neural basis regulating drug-induced compulsive behavior, and to elucidate the underlying neuro-molecular mechanisms. For our study, we established cocaine self-administration paradigm to associate behavior and cocaine reward using fixed-ratio schedule(FR) in rodents, and assessed compulsive behavior on cocaine reward combined with probabilistic foot shock. Mice were categorized into compulsive (shock-resistant) and non-compulsive (shock-sensitive) groups, and we identified distinct neural activation of Parasubthalamic nucleus(PSTN) in the compulsive group. PSTN activation by cocaine was further confirmed by Ca2+ dependent activity measurements. To determine the causal role of PSTN neurons in compulsive behavior, we applied optogenetic and chemogenetic strategies to manipulate PSTN neuronal activity. Activation of PSTN neurons induced compulsive-like behavior even in the absence of cocaine, indicating a direct contribution of PSTN activity to

compulsive responding. Furthermore, single-cell RNA sequencing revealed upregulation of 5-HT receptors specifically in the compulsive group, suggesting serotonergic modulation as a potential mechanism. The conditional knockout of 5-HT receptor in PSTN showed a reduced proportion of compulsive animals, confirming its functional relevance. Collectively, our findings identify the PSTN as a critical neural substrate underlying cocaine addiction, providing new insights into molecular mechanism driving maladaptive drug consumption in a compulsive manner.

Disclosures: T. Kim: None. **S. Lee:** None. **S. Choi:** None. **J. Shin:** None. **J. Pyo:** None. **J. Kim:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.17/KK6

Topic: H.08. Drugs of Abuse and Addiction

Title: Novel Regulation of Dopaminergic Nuerotransmission by Selective Autophagy of the Dopamine Transporter

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Abstract: The dopamine transporter (DAT) is one of the major determinants of dopamine signaling. We have previously shown that autophagy, or self-eating, selectively targets DAT for degradation, suggesting that autophagy regulates dopamine signaling. However, the molecular mechanism of selective targeting of DAT by autophagy is unknown. Selective autophagy uses various eat-me signals to recognize its cargo. One of these signals is the pentapeptide KFERQ motif. Using bioinformatics, we have identified a previously uncharacterized selective autophagy motif in the N-terminal cytoplasmic domain of DAT. We used CRISPR/Cas9 to introduce a point mutation in endogenous DAT rendering it resistant to selective autophagy. Male but not female selective autophagy resistant DAT mice demonstrate an increase of DAT in dopaminergic nerve terminals compared to WT controls in the nucleus accumbens (NAc). Locomotor activity evaluation on selective autophagy resistant DAT mice reveals a decrease in locomotor activity in males but not female mice, suggesting that the increase in DAT protein is functional. Locomotor coordination evaluation of selective autophagy resistant DAT mice show no difference compared to WT controls. Additionally, muscle strength does not seem to be affected by the motif change. We assess the effect of selective autophagy DAT mutation on the acquisition, extinction, and reinstatement of cocaine self-administration in mice. Our findings uncover a novel mechanism by which selective autophagy regulates dopaminergic neurotransmission.

Disclosures: A. Bustos: None. **D. Sidibe:** None. **J.F. Cheer:** None. **M.M. Harraz:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.18/KK7

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DP1 DA058362

Title: Targeting mitochondrial calcium activity in mesolimbic dopamine neurons modulates reward behaviors in mice

Authors: E. M. BANYAS, *A. ABRAHAM;
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Abstract: No medications are clinically available for treating stimulant use disorders. Cocaine increases intracellular calcium activity in mesolimbic dopamine neurons, which can lead to entry of calcium into mitochondria to regulate oxidative phosphorylation. Our studies examine how a key regulator of calcium influx into mitochondria, the mitochondrial calcium uniporter (MCU) complex, influences neural activity and cocaine-mediated learning. We hypothesize that cocaine exposure increases mitochondrial calcium influx through the MCU complex in dopamine neurons to regulate drug-related learning. Our experiments target modulatory subunits of the MCU complex, mitochondrial calcium uptake proteins 1 and 3 (MICU1 and MICU3), as well as a phospholipid involved in stability of the MCU complex, cardiolipin. Male and female C57BL/6 or DAT-IRES-Cre (DAT^{Cre}) mice were used in these studies. DAT^{Cre} mice received AAV-DIO-CRISPR in the ventral tegmental area to selectively knock out MICU1 or MICU3 and were then tested in cocaine conditioned place preference (CPP), cocaine locomotor sensitization (LS), open field (OFT) and elevated plus maze (EPM) tests. Mice did not show significant baseline behavioral deficits following knockdown of MICU1 or MICU3 in dopamine neurons, but did increase anxiety-like responses in EPM. Ongoing studies suggest increased cocaine CPP in MICU3 compared to control mice and altered acquisition of cocaine LS. We then aimed to identify compounds that could modulate mitochondrial calcium in vivo. Using a HeLa cell line expressing a mitochondrially-targeted aequorin calcium sensor, we tested several compounds to determine their effects on mitochondrial calcium uptake. Compounds that showed direct modulatory effects on mitochondrial calcium (MCU-i4; duloxetine) and a mitochondrial membrane (cardiolipin) stabilizing small peptide (SS-31) were tested and found to have effects on multiple behaviors, including locomotor behavior, cocaine CPP, cocaine LS, EPM, OFT, and operant sucrose pellet responding. Our studies indicate that genetically or pharmacologically modulating mitochondrial calcium activity could affect locomotor behaviors, anxiety-like behaviors, cocaine-mediated behaviors, and operant sucrose responding, but the specific neural mechanisms underlying these effects are still under investigation. Together, these studies aim to advance therapeutic strategies for treating cocaine use disorders and other disorders through modulating mitochondrial function.

Disclosures: E.M. Banyas: None. **A. Abraham:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.19/KK8

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA053070
R21DA060354

Title: Astrocytic Calcium Signaling Differentially Regulates Cocaine-Related Behaviors Across Dorsal Striatal Subregions

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Abstract: Emerging evidence has recognized astrocytes as active regulators of neural circuit function and addiction-related behaviors. Astrocytes modulate neuronal excitability, neurotransmitter homeostasis, and synaptic transmission within brain regions implicated in substance use disorders. These functions are thought to be mediated through Ca^{2+}-dependent signaling. Although growing evidence suggests that astrocytic signaling contributes to cocaine-seeking behavior, the specific role of astrocytic Ca^{2+} dynamics within dorsal striatal circuits remains poorly understood. To address this gap in knowledge, we suppressed astrocytic Ca^{2+} signaling through selective overexpression of the plasma membrane Ca^{2+} ATPase pump (hPMCA) in astrocytes throughout the dorsal striatum (DS) of rats trained to self-administer cocaine or saline. DS-wide suppression of astrocytic Ca^{2+} significantly increased cocaine self-administration and enhanced cue-induced reinstatement of cocaine-seeking compared to control animals. Ex vivo neuronal Ca^{2+} imaging using GCaMP6f revealed increased amplitudes of neuronal Ca^{2+} transients following astrocytic suppression in cocaine-seeking animals, suggesting increased neuronal activity after disruption of astrocytic Ca^{2+} signaling. To determine whether these effects arise from specific dorsal striatal subregions, we bilaterally manipulated astrocytic Ca^{2+} signaling within the dorsomedial striatum (DMS) using either suppression via hPMCA or activation via GqDREADD. In contrast to our DS-wide suppression, DMS astrocyte suppression significantly reduced cocaine self-administration. However, DMS astrocyte manipulations did not alter cue-induced reinstatement behavior. Using fiber photometry, we recorded neuronal Ca^{2+} dynamics in vivo during active lever pressing and observed no notable alterations in neuronal Ca^{2+} signaling in cocaine-exposed hPMCA animals compared to GqDREADD and control groups. Next, we selectively manipulated astrocytic Ca^{2+} signaling within the dorsolateral striatum (DLS). Interestingly, targeting the DLS resulted in an opposing pattern, whereby astrocytic Ca^{2+} suppression increased cocaine self-administration without affecting cue-induced reinstatement. Ongoing studies are examining how DLS astrocyte Ca^{2+} signaling influences

neuronal activity associated with cocaine-seeking behaviors. Collectively, these findings reveal region-specific roles for astrocytic Ca^{2+} signaling within dorsal striatal circuits and suggest that astrocytes differentially regulate cocaine-taking and cocaine-seeking behaviors through distinct DMS and DLS mechanisms.

Disclosures: N. Tavakoli: None. **F. Wu:** None. **P.I. Ortinski:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.20/KK9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIMES University
IUF Institut Universitaire de France

Title: 5-HT4R as a Gatekeeper of Plasticity: From cAMP CREB-Driven Cocaine Dependence to Adult Stress Resilience

Authors: *V. COMPAN[1,2];
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Abstract: Across reward- and stress-related circuits, 5-HT4R signaling supports cAMP CREB-mediated gene expression and dendritic spine maintenance-maturation. In the nucleus accumbens, cocaine engages a cAMP - pCREB cascade that promotes long-lasting transcriptional changes (e.g., FosB ΔFosB) and leads to morphological remodeling. When 5-HT4Rs are absent, cocaine cannot robustly increase cAMP and pCREB, attenuating FosB ΔFosB induction, elevating permissive epigenetic signaling (G9a), and resulting in fewer dendritic spines. Results align with reduced cocaine dependence. In the same 5-HT4R KO model, reduced synaptic dendritic spine support also coincides with altered motivation, favoring food intake under chronic restriction rather than cocaine seeking. Complementing this reward mechanism, stress-related behavior is also related to 5-HT4R-dependent circuitry: restoring 5-HT4R expression in adulthood in the mPFC rescues stress-induced hypophagia via a mPFC-dorsal raphe glutamatergic pathway, indicating that the system can be rapidly re-tuned. Although baseline synaptic architecture is compromised in 5-HT4R KO mice (reduced mPFC dendritic spine density, with lower BDNF and ICAM5, consistent with impaired glutamatergic spine maturation), the ability of adult restoration to quickly normalize stress-related outcomes suggests that these behaviors are driven primarily by rapid functional circuit modulation, not by requiring an already fully established developmental synaptic wiring pattern.

Disclosures: V. Compan: None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.21/KK10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 2R01 DA029718
NIH Grant R21DA042597
NIH's Intramural Program of NIAAA

Title: Glucagon-like peptide-1 receptor agonist (GLP-1 RA) modulates neuronal and hemodynamic responses to cocaine

Authors: *H. JEONG[1], Y. PAN[1], N. D. VOLKOW[2], C. DU[1];
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Abstract: Cocaine exposure damages the brain by reducing cerebral blood flow and blood oxygenation while increasing intracellular Ca^{2+} transients in neurons. While glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are established metabolic regulators clinically approved for type-2 diabetes and obesity, emerging evidence suggests that they also modulate drug-seeking behavior and provide neural and vascular protection. However, their precise impact on the neurovascular system remains unexplored. Here, we examined the effects of acute administration of a GLP-1 RA dulaglutide on cocaine-influenced alterations in cortical vasculature and neuronal activity using *in vivo* wide-field fluorescence imaging and optical coherence tomography in the living mouse cortex. Our data revealed that dulaglutide treatment increased baseline blood flow by dilating both cortical veins and arteries, effectively rescuing cocaine-induced hypoperfusion. Precise tracking of individual vessels demonstrated that cocaine-evoked vasoconstriction and subsequent flow rate decline were significantly minimized when the dulaglutide was administered one hour prior to cocaine exposure. Furthermore, dulaglutide attenuated intracellular neuronal Ca^{2+} levels, reducing cocaine-induced neuronal Ca^{2+} accumulations that underlies addiction-related plasticity. Together, these findings show that clinically approved GLP-1 RAs protect against cocaine-induced neurovascular toxicity and highlight their potential to be repurposed as a therapeutic strategy for cocaine use disorder.

Disclosures: H. Jeong: None. **Y. Pan:** None. **N.D. Volkow:** None. **C. Du:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.22/KK11

Topic: H.08. Drugs of Abuse and Addiction

Title: Nucleus accumbens amylin receptors modulate cocaine behaviors in a sex-dependent manner

Authors: *R. PETRILLI FORTUNA[1], A. CAFFREY[1], H. D. SCHMIDT[2];
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Abstract: Cocaine use disorder (CUD) is a chronic, relapsing condition that remains a major public health concern. Currently, there are no FDA-approved pharmacotherapies to treat CUD, highlighting the need to identify novel druggable treatments. One promising candidate is amylin, a peptide hormone that acts on amylin receptors (AMYRs) to modulate feeding and satiety. Central AMYR activation reduces motivated food intake and decreases the hedonic value of palatable food, in part, by modulating the mesolimbic dopamine system. Addictive substances exert their rewarding effects by increasing dopamine release into the nucleus accumbens (NAc). These mechanistic and regional overlaps prompted investigations into the role of AMYR activation in addiction-like behaviors. Using a non-selective AMYR and calcitonin receptor agonist, salmon calcitonin (sCT), studies showed that peripheral and central AMYR activation attenuates both behavioral and molecular responses to alcohol and cocaine in rodent models. However, the specific contribution of AMYRs to these effects remains unknown. To directly test whether NAc AMYRs modulate cocaine-related behaviors, we examined the effects of the endogenous AMYR ligand amylin infused into the NAc shell. Male (n=13) and female (n=7) rats were implanted with jugular catheters and guide cannulae targeting the NAc shell. After 7 days of recovery, rats were allowed to self-administer cocaine (0.245 mg/infusion). After 21 days of cocaine self-administration sessions, rats were pretreated with intra-NAc shell infusions of amylin (0, 0.04, or 0.4 μg). Intra-NAc amylin significantly attenuated cocaine self-administration in male, but not female, rats, revealing a sex-dependent modulation of cocaine taking at the doses tested. After the self-administration phase, cocaine taking was extinguished. Rats were then pretreated with intra-NAc amylin before a cocaine priming injection (10 mg/kg, i.p.) and tested for reinstatement. Under these conditions, intra-NAc amylin robustly reduced cocaine-primed reinstatement in both male and female rats. The sex differences observed during cocaine self-administration, but not during reinstatement, suggest that NAc AMYR activation may engage distinct downstream mechanisms depending on the behavioral state. Collectively, these findings demonstrate that exogenous amylin acting at NAc shell AMYRs suppresses both voluntary cocaine taking and seeking, identifying central AMYRs as a potential therapeutic target for reducing cocaine seeking during abstinence.

Disclosures: R. Petrilli Fortuna: None. **A. Caffrey:** None. **H.D. Schmidt:** None.

Poster

PSTR284: Cocaine: Cell Signaling, Plasticity, Circuitry, and Glial Mechanisms

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR284.23/KK12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R21DA058205

Title: The effect of chemogenetic manipulation of oxytocin neurons in the paraventricular nucleus of the hypothalamus on cocaine preference behavior

Authors: *K. WOLFHOPE[1], K.-C. LEONG[2];
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Abstract: Cocaine use disorder (CUD) is a chronic, debilitating condition with limited treatment options. Oxytocin (OXT), a neuropeptide produced in the paraventricular nucleus (PVN) of the hypothalamus, has emerged as a potential therapeutic avenue for CUD. Previous work from our laboratory has demonstrated that OXT administered peripherally is capable of attenuating cocaine conditioned place preference (CPP) behavior; however, it remains unclear whether manipulation of endogenous OXT signaling may also mediate this therapeutic effect on cocaine CPP. In the present study, we examine how designer receptors exclusively activated by designer drugs (DREADD)-mediated activation and inhibition of oxytocin neurons in the PVN alters cocaine preference behavior in a CPP paradigm. Male and female Long-Evans rats (n = 48) received bilateral infusions of excitatory (OXT-HM3Dq) or inhibitory (OXT-HM4Di) DREADD virus expressed through the OXT promoter into the PVN. Following a 3-week incubation period, animals underwent the 10-day CPP paradigm. Rats were conditioned with cocaine (10 mg/kg) and received either vehicle (VEH) or Clozapine N-oxide (CNO; 3 mg/kg) at test. Cocaine CPP was assessed by the percent of time spent in the drug-paired chamber and analyzed using a two-way ANOVA. While animals receiving VEH at test displayed significant preference for the cocaine-conditioned chamber, CNO-mediated activation of OXT Gq or Gi DREADD resulted in disruption of this effect. This suggests that endogenous PVN OXT modulates cocaine CPP. These findings provide mechanistic insight into the role of oxytocin neurons in the PVN in modulating cocaine preference behavior and sheds light into the ability for endogenous OXT to modulate cocaine reward.

Disclosures: K. Wolfhope: None. **K. Leong:** None.

Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.01/KK13

Topic: I.03. Decision Making

Support: Wellcome Trust 224432/Z/21/Z
NIH T32GM007753
NIH T32GM144273

Title: Lateralized contributions of dorsolateral prefrontal cortex area 46 to approach-avoidance decision-making

Authors: *J. M. PHAN[1,2], X. ZHANG[1], C. M. WOOD[1], A. C. ROBERTS[1];
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Abstract: Impaired decision-making under conflict between positive and negative outcomes is a hallmark of many neuropsychiatric conditions, including depression, anxiety, and addiction. Human neuroimaging studies and non-human primate electrophysiological studies implicate the dorsolateral prefrontal cortex (dlPFC) in regulating behavior in such conditions (Rolle et al., 2021; Amemori et al., 2015), yet its causal contribution remains poorly understood. Neuroimaging studies further suggest that the left and right dlPFC may play distinct, and potentially opposing, roles in processing reward- and aversion-related information (Zorowitz et al., 2020; Chrysikou et al., 2016; Spielberg et al., 2014). Consistent with this idea, recent work from our laboratory demonstrated a causal role for left, but not right, dlPFC area 46 (dlPFC-46) in appetitive motivation and responses to uncertain threat (Wood et al., 2025). Here, to determine the causal contribution of dlPFC-46 to approach-avoidance decision-making, we developed a touchscreen-based task for common marmosets (*Callithrix jacchus*). Animals responded on two positively reinforced options operating under independent variable-interval schedules. Behavioral probes assessed responsivity to either high-reward conditions alone or aversive outcomes (darkness and white noise) in low-conflict (baseline reward) or high-conflict (high reward) conditions. Temporary inactivation of dlPFC-46 was achieved using bilateral or unilateral intra-dlPFC-46 infusions of the GABA-A and GABA-B receptor agonists muscimol and baclofen. Under baseline conditions, animals distributed responses across both options to maximize reward. Increased reward reliably shifted responding toward the high-reward option, whereas aversive outcomes reduced responding on the aversive option. Inactivation of dlPFC-46 altered responses to both appetitive and aversive contingencies. Left-sided or bilateral inactivation enhanced responsivity to unexpected high reward. In contrast, responses to unexpected aversive outcomes relied on coordinated bilateral dlPFC-46 function. Together, these findings suggest a left-lateralized or bilateral role for dlPFC-46 in reward processing and a bilateral role in regulating responses to aversive outcomes. Ongoing work will integrate these behavioral findings with computational modeling to better define the mechanisms by which dlPFC-46 supports decision-making under motivational conflict, with implications for neuropsychiatric conditions characterized by maladaptive decision-making.

Disclosures: J.M. Phan: None. **X. Zhang:** None. **C.M. Wood:** None. **A.C. Roberts:** None.

Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.02/KK14

Topic: I.03. Decision Making

Title: Parallel prefrontal ensembles encode competing cognitive rules

Authors: *X. LI, H. KWON;
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Abstract: The medial prefrontal cortex (mPFC) is widely recognized for its essential role in cognitive flexibility. However, mechanisms underlying flexible categorization at neuronal and circuit levels remain largely unknown. We designed a flexible categorization task for freely moving mice, where mice were required to report a choice between two visual stimuli with different shapes presented at different vertical locations. After learning two distinct rules, fully trained mice could switch multiple times between the object rule and the height rule. Mice maintained consistently high performance of congruent trials across multiple blocks, whereas rule switch typically led to a rapid drop of incongruent trial performance. Suppressing mPFC activity via chemogenetic inhibition significantly impaired the rule-switching performance, resulting in more trials to reach the switch criterion and a reduced fraction of correct incongruent trials, while performance of congruent trials was not affected, indicating that the decline in performance was due to cognitive impairment rather than sensory deficits. Through cell-type-specific chemogenetic inactivation, we found that parvalbumin-expressing (PV) interneurons in mPFC were necessary for this task, whereas prefrontal somatostatin-expressing (SST) interneurons and vasoactive-intestinal-peptide-expressing (VIP) interneurons were not. To investigate how mPFC encodes rule-relevant information, we performed in vivo miniscope calcium imaging to record individual neuronal activity during the task. We identified rule-selective neurons with significantly different levels of activity between object and height rules. The temporal activity patterns of rule-selective neurons were highly heterogenous. Dimensionality reduction of trial-averaged activity across all recorded neurons revealed that the distance between neural trajectories associated with the object and height rules was significantly greater than in shuffled controls, indicating population-level separation of neural representations for competing rules in the mPFC. We further applied ST-Cal-Light to selectively label neurons active during rule execution with high spatiotemporal precision. Optogenetic inhibition of tagged neurons lowered the accuracy of incongruent trials during the labeled rule task but had no effect on the opposite rule, suggesting independent neural ensembles encode different rules without direct mutual interference. These findings can extend our knowledge about how mPFC supports flexible categorization and may also shed light on the general mechanism of high-level cognitive functions.

Disclosures: X. Li: None. **H. Kwon:** None.

Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.03/KK15

Topic: I.03. Decision Making

Support: Career Development Award IK2BX0006125 to M.F.K.

Title: Cortico-striatal white matter tract health associated with chronic deficits in reward-guided behavior post-TBI

Authors: *B. NEWTON;
UCSD, San Diego, CA

Abstract: Patients with a TBI are 3 times more likely to develop a neuropsychiatric disorder but current treatment strategies do not address chronic cognitive impairments contributing to this increased risk. To better assess injury-induced changes in reward evaluation and decision-making we used a bi-frontal controlled cortical impact (CCI) in rodents that reliably results in reward learning deficits. In 30 adult Long-evans rats, we measured behavior on a probabilistic reversal learning task (PRL), dependent on the prefrontal cortex and its striatal connections for reward discrimination, valuation, and behavioral flexibility. During the PRL task, rats choose between a high probability reward (80%) or a low probability reward (20%) and contingencies reverse when 8/10 responses are high probability. Behavior on the PRL task was compared to structural integrity of white matter tracts measured from ex-vivo diffusion tensor imaging (DTI) scans 12 weeks post-injury. DTI metrics like quantitative anisotropy (reflecting axonal degradation) were different between groups (ANOVA) measured in the whole brain ($F(2,21)=3.68$, $p=0.043$), prefrontal cortex (PFC) ($F(2,21)=6.24$, $p=0.007$), striatum ($F(2,21)=4.08$, $p=0.032$), and the connections between PFC and striatum ($F(2,21)=4.60$, $p=0.022$). Subsequently, a combinatorial z-score x Mahalanobis distance analysis indicated that the severe TBI distribution of DTI metrics in PFC was significantly higher than controls ($p=0.023$). The structural changes between groups were also related to behavioral performance. Quantitative anisotropy ($\rho= -0.453$, $p=0.03$), mean diffusivity ($\rho= -0.523$, $p=0.01$), and radial diffusivity ($\rho= -0.421$, $p=0.045$) were negatively associated with the average number of reversals each subject completed. Our results suggest that cortico-striatal white matter tract damage may explain behavioral impairments in decision-making and provide evidence of structural reorganization following frontal TBI.

Disclosures: B. Newton: None.

Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.04/KK16

Topic: I.03. Decision Making

Support: ERC
Wellcome Trust

Title: Frontal cortical lateralization is shaped by choice bias and sensory evidence

Authors: *H. ATILGAN, Y. SHEVCHUK, M. TVRDIC, M. LYNN, A. LAK;
Univ. of Oxford, Oxford, United Kingdom

Abstract: Decision-making relies on the integration of incoming sensory signals and internal choice biases. Dorsal medial frontal cortex (dmFC) neurons encode stimuli and actions in a lateralized manner, often exhibiting stronger responses to contralateral stimuli and actions. However, it remains unclear whether these lateralized representations reflect the integration of sensory evidence and choice bias during decision-making. To address this question, we recorded activity of excitatory neuronal populations across the dmFC using two-photon microscopy in transgenic head-fixed mice performing a two-alternative visual decision-making task. Recordings obtained from the left and right hemispheres revealed lateralized representations of task-relevant variables, with stronger encoding of contralateral compared to ipsilateral stimuli. To determine how these neuronal signals represent sensory evidence and choice bias, we examined sessions exhibiting ipsilateral or contralateral choice biases. We then further classified these sessions according to the relative weights animals gave to ipsilateral and contralateral visual stimuli, inferred from session-by-session psychometric curves. Sessions in which animals assigned comparable weights to ipsilateral and contralateral stimuli exhibited larger neuronal lateralization. However, sessions characterized by asymmetric sensory weighting showed reduced dmFC neuronal lateralization. This effect was strongest in sessions with contralateral choice biases, suggesting that dmFC lateralized representations reflect an interaction between internal choice bias and the use of sensory evidence. Together, these findings reveal that lateralized neuronal representations in dmFC are shaped by choice bias and sensory evidence. They suggest that frontal cortical lateralization provides an organizational structure through which perceptual and motor signals interact to shape decision-making.

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Poster

PSTR285: Prefrontal Cortex and Decision-Making

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Program #/Poster #: PSTR285.05/KK17

Topic: I.03. Decision Making

Support: NIMH Grant MH136708

Title: Sex and Corticostriatal Subcircuits Regulate Specific Behavioral Control Strategies and Stress-Related Pathology

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Abstract: Neuropsychiatric disorders and chronic stress exposure exhibit several overlapping symptomologies, including impaired cognitive control over behavior. Because disease risk is heavily impacted by stress exposure, increasing our understanding of how stress broadly impacts cognitive constructs, what neural circuits regulate these constructs, and how they are altered by stress has important implications for reducing disease susceptibility. Our past findings show that chronic unpredictable stress (CUS) impairs cognitive flexibility in male, but not female mice during a strategy shift task (SST). The current body of work using adolescent male and female mice combined a model of CUS with chemogenetic manipulation of prelimbic D1- and D2-projections to the nucleus accumbens (NAc), and measures of flexibility, impulse control (5-choice serial reaction task, 5-CSRT), and risk behavior (Iowa Gambling Task, rlGT) to further investigate the differential effects of CUS on cognition. Data indicate that while global inhibition of the PLC-NAc circuit (n=33) does not impact flexibility in either sex, inhibition of D2-NAc circuits (n=28) impairs flexibility in males, while inhibiting D1-NAc (n=28) improves flexibility in females. Further, results indicate that CUS deficits in males can be rescued by activation of D2-NAc circuits or by global activation of the prelimbic cortex (n=31). In contrast to previous findings with SST, CUS increased impulsive behavior in females but not males and negatively impacted decision-making behavior in both sexes (n=32 for 5-CSRT and n=32 for rIGT). Similar to previous studies with SST, however, CUS had no effect on the ability of animals to learn behavioral tasks like 5-CSRT and rIGT. Ongoing work is examining the role D1- and D2-NAc circuits play in impulse control and CUS-related deficits, how D1 and D2-NAc circuit activity is altered during stress and engagement in cognitive flexibility using Miniscopes, and how cognitive control strategies work together using a modified rIGT. These data highlight potential fundamental sex differences in neural circuits utilized during behavioral control and indicate that CUS uniquely impacts cognitive constructs across sex.

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Poster

PSTR285: Prefrontal Cortex and Decision-Making

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Title: Strain-dependent sensitivity to psychostimulant-induced modulation of risky choice preference in Fischer-344 and Long Evans rats

Authors: *S. A. DE GUZMAN, C. KNAPP, B. D. WATERHOUSE, R. L. NAVARRA;
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Abstract: Catecholamine neurotransmitter systems, dopamine (DA) and norepinephrine (NE), regulate prefrontal cortex (PFC)-mediated executive functions. Dysregulation of these systems contributes to neuropsychiatric and neurodegenerative conditions marked by maladaptive risk-taking behavior, such as attention-deficit/hyperactivity disorder (ADHD), substance use disorder, and Alzheimer's disease (AD). This convergence highlights the translational potential of ADHD therapeutics, particularly the DA/NE-enhancing psychostimulants methylphenidate (MPH) and amphetamine (AMPH) and the selective NE reuptake inhibitor atomoxetine (ATX), for modulating AD-related behavioral dysfunction. Evidence further implicates mesocorticolimbic dopaminergic signaling in psychostimulant-induced alterations in reward valuation and risky choice. Drug-class-specific effects on risky choice have been demonstrated in Long Evans (LE) rats but have not yet been characterized in Fischer-344 (F344) rats, the background strain of the TgF344-AD model. This gap limits interpretation of catecholaminergic manipulations and raises the possibility of strain-dependent differences in drug sensitivity. Using the probabilistic discounting task (PDT), in which rats choose between a small/certain reward and a large/risky reward delivered at decreasing probabilities, we compared the effects of intraperitoneal MPH (2-8 mg/kg), AMPH (0.25-1 mg/kg), and ATX (0.3-1 mg/kg) on decision making in LE and F344 rats. Psychostimulants increased preference for the large/risky option in both strains, but these effects were attenuated in F344 rats. ATX did not alter choice behavior in either strain. Together, these findings indicate reduced sensitivity of F344 rats to psychostimulant-induced increases in risky choice, consistent with potential strain-dependent differences in dopaminergic modulation of risk/reward decision making. This profile establishes a critical benchmark for interpreting catecholaminergic manipulations in F344-based disease models, including TgF344-AD. Future studies will extend this work to additional receptor-specific agents to further delineate strain-specific differences in sensitivity to pharmacologically induced alterations in decision making to improve cross-study comparability and translational inference.

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Poster

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Topic: I.03. Decision Making

Support: AFOSR FA9550-24-1-0288

Title: Cognitive flexibility exacts a measurable neural energy cost in prefrontal cortex

Authors: *E. M. GRIGSBY[1], C. MEDEIROS[1], E. OZANICK[2], N. MAGEN[1], M. T. ZENNOUCHE[1], B. A. EBITZ[1];
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Abstract: Cognitive flexibility is both fundamental to intelligent behavior in dynamic environments and costly to initiate and sustain. Identifying the physiological bases of these costs may be the key to understanding and treating disorders in which cognitive flexibility is compromised. While behavioral modeling suggests that cognitive flexibility is more energetically costly than rigid or consistent behavior, no study has directly linked the energetic costs of flexible behavior to cortical neural activity. Here, we leveraged tools from statistical mechanics to measure the dynamics of behavior in a rule-switching task and infer the energy required to initiate and occupy flexible brain states. We then examined how these behavioral energy predictions related to population neural activity in the dorsolateral prefrontal cortex (dlPFC) of rhesus macaques (n=2) performing the rule-switching task. We found that flexible states bore the hallmarks of an energetically demanding process, characterized by high maintenance costs and rapid depletion. Consequently, despite being entered frequently, the total time spent occupying these unstable states was strictly limited. Crucially, flexible states were associated with a distributed increase in spiking activity across neurons, and neural activity peaked at precisely the times predicted by our statistical model: during flexible brain states and at transitions between flexible and inflexible brain states, regardless of direction. Finally, there was a striking correlation between the energy demand predicted from behavior and session-by-session variability in dlPFC spiking activity. By providing a direct link between statistical measures of behavioral energetics and prefrontal spiking activity, these results establish a mechanistic account of why cognitive flexibility is particularly energy-demanding. They demonstrate that the prefrontal cortex pays outsized neurometabolic costs of initiating and maintaining these flexible brain states. This frames flexible behavior as a metabolic trade-off, where computational versatility is directly constrained by, and therefore vulnerable to, real-time energetic limits.

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Poster

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Topic: I.03. Decision Making

Support: NIH Grant DA062121

Title: Prelimbic Cortex Modulates Action Sequences, But Not Decision Variables, During Perceptual Decisions In Rats

Authors: *K. CHAVEZ LOPEZ, J. BLACKMER, M. LAUBACH;
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Abstract: We trained rats to perform a visual detection task with three levels of cue luminance (Palmer et al., bioRxiv 2025.10.25.684539). The stimulus remained active only while the rat maintained a nose poke in the center port. Consequently, shorter sampling times limited evidence accumulation and increased errors. Drift Diffusion Models (HSSM) revealed that drift rate depended on cue luminance and threshold varied with self-determined sampling times. Sampling behavior thus modulates the decision process. We next used pose estimation (SLEAP) to examine movement. Linear and angular velocity during the initiation of choice were sensitive to cue luminance and to outcome (hits or misses). A time-series classifier (MultiRocket, with extensions from I-ROCKET) identified the time points at which movement signals tracked luminance. Predictive features spanned the entire action sequence, from the start of the trial to the initiation of reward retrieval. We used the kinematic measures as regressors in drift-diffusion models, and found that higher velocities were associated with higher drift rates and lower decision thresholds. We then used reversible inactivations to study the prelimbic cortex (PLC). Inactivation did not affect decision-related measures, contrasting with our group's previous finding that it does influence value-based decisions (Palmer et al., PMID: 39327005). Kinematic analysis showed that inactivation of PLC changed the timing and increased the variability of the linear and angular velocities in all rats relative to PBS controls. I-ROCKET classified velocity traces by experimental condition (PBS vs. muscimol) with >75% accuracy. While locomotion was preserved, all rats showed disruptions in the kinematics of the choice response, specifically the angular velocity of the orienting turn towards one of the choice ports. Our findings suggest that the prelimbic cortex influences the execution of action independent of the decision-making process.

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Poster

PSTR285: Prefrontal Cortex and Decision-Making

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P30 EY001583

Title: Exploring the roles of primate Frontal Eye Field (FEF) in representing decision bounds

Authors: *J. BHATTI[1], J. I. GOLD[2], L. DING[2];
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Abstract: A fundamental question in neuroscience is how the brain uses visual information to make appropriate decisions. A key component of the decision-making process is a decision rule that terminates deliberation and results in decision commitment. In the accumulation-to-bound framework, which captures human and animal decision performance in many tasks, the decision rule is implemented as comparisons between the accumulated evidence and decision bounds associated with different alternatives. For oculomotor decisions, activity in FEF, LIP, and SC converges to a common level just prior to decision-indicating saccades, possibly reflecting bound crossings. However, because the actual bounds can only be estimated as an average across many tens of trials in those earlier studies, the association between these pre-saccade activity and decision bounds remains unclear. We recently developed a novel task that allows trial-by-trial measurements of decision bounds. In this task, the decision variable (DV) is presented directly in the form of the position of a visual cue. The cue (a circular spot) moves at a rate of one step per 50ms, where the size of each step is drawn from a gaussian distribution with a fixed variance. For each trial, the mean step size is chosen randomly from a set of 8 possible values (4 per direction, +/- values for left/right motion) that determines how quickly the cue tends to approach one target or the other. Task difficulty is controlled by the mean step size and the variance. The monkey reports its decision with a saccadic eye movement to one of the two choice targets. The cue position at the time of decision commitment is interpreted as bound height at bound crossing. We examined the activity of 112 FEF neurons from one monkey performing the novel task. We measured average firing rates in eight 100ms windows from cue onset to saccade onset and computed correlations with bound height across trials. Activity of 64 neurons was correlated with the bound magnitude in at least one window. Of these, 18 and 10 neurons showed positive and negative correlations, respectively, only for contralateral choices; 9 and 11 neurons showed positive and negative correlation, respectively, only for ipsilateral choices; 16 neurons showed a correlation for both choices, of which 9 were positive relationships, 2 were negative, and the remaining 5 showed opposite modulation between choices. These preliminary results suggest that FEF may be closely and flexibly involved in the implementation of decision rules.

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Poster

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Topic: I.03. Decision Making

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Title: Do fast and slow learners differ in how they learn novel concepts? An EEG study

Authors: *L. CHANG[1], A. FARAHBOD[1], Y. JUNG[1], N. STEINBERG[1], F. A. MARTINEZ-ADDIEGO[1], T. MORGAN[2], P. BANDETTINI[2], M. RIESENHUBER[1];

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Abstract: We recently presented evidence that learning of a novel categorization in humans (here of morphed car stimuli) initially involves learning a task representation in prefrontal cortex (PFC), followed by later transfer to temporal cortex as the task becomes automated (Cox et al., JoCN, 2026). While our previous study only performed neural recordings before and after extensive training, to investigate the hypothesis of transfer of task knowledge out of PFC, we trained typical adults (N=25) on a simplified version of the visual concept learning task while performing high-density (128 channel) EEG recordings in one recording session consisting of 3 blocks of 320 trials each (Chang et al., SFN, 2025). Here, we investigated the neural bases of differences in task learning speed. Participants were split into 2 groups based on how quickly they learned the task: "fast" learners performed above 85% accuracy discriminating morphed cars by the second half of block 1 (N=15), and "slow" learners performed below the cutoff (N=10). Fast learners had significantly higher accuracy than slow learners (blocks 1-2 and the first half of block 3 for prototypes and within-boundary morphs, $P<0.05$; all 3 blocks for across-boundary morphs, $P<0.01$). We hypothesized that the behavioral differences were reflected at the neural level—in particular, engagement of PFC for initial learning differs between the fast and slow learner groups. To test our hypothesis, we localized select frontal, temporal, and parietal channels to represent our three regions of interest. Representational similarity analyses (RSA) indicated greater discrimination of stimuli belonging to different categories in the frontal sensor group for fast learners, persisting across blocks 1 and 2, and then interestingly in parietal sensors in block 3 while selectivity in frontal sensors declined. Granger causality (GC) analyses showed an increase in GC from frontal to parietal sensors in block 3 compared to the first two blocks only for fast learners, suggesting task transfer to parietal cortex. In addition, there was also the previously found increase in GC with temporal channels and RSA evidence for temporal selectivity in block 3. In contrast, in slow learners, frontal selectivity increases occurred later, in blocks 2 and 3, followed by a selectivity increase in temporal channels in block 3. GC for slow learners was significantly greater in block 2 from frontal to temporal. Yet, slow learners did not show evidence for engagement of parietal areas. Taken together, these results provide preliminary evidence that fast learners do not just engage frontal and temporal cortex but also show evidence for task transfer to parietal areas.

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Poster

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Title: Changes in firing rate activity and increased dopamine release in the prelimbic cortex correlate with risky behavioral choice during an approach-avoidance conflict test in rats

Authors: *V. CHUONG, G. AQUINO-MIRANDA, E. L. BOLING, F. H. DO MONTE; Neurobio. and Anat., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Adaptive decision-making requires evaluating competing environmental cues and adjusting behavioral strategies to changing contexts. The prelimbic (PL) subregion of the medial prefrontal cortex (mPFC) is essential for contextual memory retrieval and is implicated in motivational conflict when reward and threat cues co-occur. However, how PL dynamically responds when animals switch from reward-approach to threat-avoidance during conflict remains unclear. PL receives direct dopaminergic inputs from the ventral tegmental area, and considering the role of dopamine in the mPFC in cognition, we hypothesized that dopamine release in PL modulates neuronal activity to shape behavioral choice during motivational conflict. To test this idea, adult Long-Evans rats were implanted with single-unit recording electrodes in PL to monitor neural activity, or optical fibers with the fluorescent dopamine sensor $GRAB_{DA}$ to quantify dopamine release. Rats trained to press a lever for food during the presentation of audiovisual cues were exposed to an approach-avoidance conflict test consisting of a reward phase (only food cues), an odor phase (only fear-inducing cat odor), and a conflict phase (food cues presented with cat odor). Compared to the reward phase, rats displayed increased defensive behaviors and reduced food-seeking responses during the odor and conflict phases. The next day, rats were returned to the same arena without cat odor to test contextual fear retrieval (context phase). In the context phase, rats showed variable responses to food cues across trials, either approaching the food area to press for food (risk-taking) or avoiding the area and not pressing (risk-avoiding). Analysis of PL activity at food-cue onset revealed similar proportions of responsive cells during risk-taking (25%) and risk-avoiding (24%) trials. However, only 7% of the cells responded in both trial types, indicating that distinct subsets of food cue-responsive PL neurons are recruited according to the rats' behavioral choice. Food cue-responsive PL cells active during risk-taking trials were attenuated during risk-avoiding trials, and vice versa, mirroring the rats' behavior. Moreover, $GRAB_{DA}$ recordings revealed robust food cue-evoked dopamine release in PL during the reward phase but not during the conflict phase. Interestingly, during the context phase, food cue-evoked dopamine responses were greater during risk-taking than risk-avoiding trials. Collectively, these findings suggest that risky behavioral choice during motivational conflict is associated with enhanced food-cue evoked responses in PL cells and elevated dopamine release in PL.

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Poster

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Topic: I.03. Decision Making

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Title: Differences in inhibitory inputs onto neurochemically distinct inhibitory interneuron subtypes in rhesus monkey prefrontal cortex

Authors: *H. BHATT[1], B. J. SNYDER[2], T. L. MOORE[1], D. L. ROSENE[1], J. I. LUEBKE[1], M. MEDALLA[1];
[1]Anat. & Neurobio., Boston Univ. Chobanian and Avedisian Sch. of Med., Boston, MA; [2]Grad. Program for Neurosci., Boston Univ. GPN, Boston, MA

Abstract: The networks within and between Lateral Prefrontal (LPFC) and Anterior Cingulate (ACC) cortices support cognitive processes that depend on coordinated activity between excitatory pyramidal neurons and local inhibitory interneurons (InNs). Distinct populations of GABAergic InNs in primates are identified based on expression of the calcium-binding proteins (CaBP), calbindin (CB), parvalbumin (PV), and calretinin (CR). Little is known about the organization of synaptic inputs and interconnectivity among these InN subtypes in monkey cortex, or whether these patterns differ across higher-order cortical regions such as the LPFC and ACC.Using immunohistochemistry and confocal microscopy in rhesus monkeys (*M. mulatta*), we confirmed that, in both LPFC AND ACC, InN subtypes differed in morphological features: CR InNs were bipolar, PV InNs were multipolar, and CB InNs were a mix of bipolar and multipolar. To assess inter-subtype InN connectivity, we examined vesicular GABAergic transporter+ (VGAT+) boutons apposed (i.e. putative synapses) to somata and dendrites of CB, PV, and CR InNs and determined the subset of these VGAT+ appositions (apps) co-expressing each CaBP. CR InNs received more dense VGAT+ apps than PV and CB, particularly in ACC (ANOVA main effect, InN type, $p < 0.05$). CB InNs received the densest CR+VGAT+ inputs, while CR and CB InNs received more dense PV+VGAT+ inputs than PV. Majority of VGAT+ apps on somata did not express any CaBP (CB-PV-CR-), particularly in PV (~81-89%) compared to CR (~65-80%) and CB (~62-66%, main effect, InN type, $p<0.05$). In both areas, the proportion of CR+VGAT+ apps was greater on CB (~21-23% of total somatic; ~28-36% of total dendritic VGAT+ apps) compared to PV (~8-16% somatic; 15-20% dendritic) and CR (<3%, $p<0.01$). The proportion of PV+VGAT+ apps was higher on CR somata (~16%) and dendrites (~20%) than on PV (<6%), especially within the LPFC ($p<0.05$). These results show that differences in VGAT+ app densities and proportions depended primarily on InN subtype. PV InNs received sparse inhibition from CaBP+ subtypes, and received strong inhibition from other subtypes not examined here. CB received substantial inhibitory inputs from all three CaBP subtypes, while CR received inhibition from CB and PV subtypes. Interestingly, both CR-to-CR and PV-to-PV inhibition were sparse. Notably, an inter-areal difference was observed only for PV+ inputs to both CB and CR dendrites, which were more dense in the LPFC than in the ACC. These findings reveal cell-type-specific InN inter-connectivity across LPFC and ACC underlying diverse local inhibitory-disinhibitory interactions that can shape cognitive network dynamics.

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Poster

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Title: Mapping spatial working memory-related intermediate early gene expression in prefrontal-premotor connections of rhesus macaques

Authors: *S. VYAS[1], H. BHATT[2], M. P. JOYCE[3], T. L. MOORE[4], M. MEDALLA[5]; [1]Boston Univ., Boston, MA; [2]Dept. of Anat. and Neurobio., Boston Univ. Chobanian and Avedisian Sch. of Med., Boston, MA; [3]Anat. & Neurobio., Chobanian & Avedisian Sch. of Medicine, Boston Univ., Boston, MA; [5]Anat. & Neurobio., [4]Boston Univ. Sch. of Med., Boston, MA

Abstract: Working memory and goal-directed behavior are supported through interactions between the lateral prefrontal cortex (LPFC), anterior cingulate cortex (ACC), and dorsal premotor cortex (PMd). Together, these regions form an executive control network that integrates cognitive processing, behavioral monitoring, motivation, and motor planning. While evidence suggests that this network supports working memory, the laminar organization of pathways linking the LPFC, ACC, and the PMd to directly support cognitive tasks remains unknown. We explored this question using neural tract tracer injections in PMd and cognitive task-activated immediate early gene (cFos) expression in young adult rhesus macaques. Macaques trained for several months on the spatial working memory Delayed Recognition Span Task (DRST), and received a surgical injection of a retrograde neural tracer in PMd about three weeks before euthanasia. The subjects performed a final testing session within three hours of euthanasia and tissue harvest. After double-label immunohistochemistry for cFos and the neural tracer, we used unbiased stereological quantification methods to quantify the regional and laminar distribution of cFos+ and PMd-projecting tracer-labeled neurons in LPFC and ACC. The results revealed regional differences in cFos distribution. About one third of cFos+ neurons were located in the LPFC (areas 9 and 46), while the rest were, for the most part, evenly distributed across the subgenual, pregenual, and dorsal parts of the ACC. By area, pregenual ACC Area 32 contained the highest proportion of cFos-positive neurons, followed by dorsal ACC Area 24, subgenual ACC Area 25, and then LPFC Area 46v. In contrast, tracer-positive neurons projecting to PMd were broadly distributed across LPFC and ACC regions without significant regional differences. Tracer+/cFos+ neurons were found in the highest proportion in the dlPFC Areas 9 and 46, but were sparse in ventral area 46. Across all examined areas, both cFos+ and tracer+ neurons were denser in deep cortical layers (V/VI), the source of diverse cortical and subcortical projections important for motor control. Overall, these findings provide insight into the laminar organization and regional activation of frontal cortical pathways linking LPFC and

ACC with premotor cortex, highlighting their contribution to the neural network supporting motor planning, working memory, and decision-making.

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Poster

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Title: Working Memory-Related c-Fos Immediate Early Gene Expression in Diverse Prefrontal Inhibitory Interneurons in Aging Monkeys

Authors: *R. Y. B. A. MUSA[1], C. A. MOJICA[1], M. P. JOYCE[2], D. L. ROSENE[3], T. L. MOORE[4], M. MEDALLA[5];
[1]Anat. & Neurobio., Boston Univ., Boston, MA; [2]Anat. & Neurobio., Chobanian & Avedisian Sch. of Medicine, Boston Univ., Boston, MA; [3]Anat. & Neurobio., Boston Univ. Grad. Program In Anat. & Neurobio., Boston, MA; [5]Anat. & Neurobio., [4]Boston Univ. Sch. of Med., Boston, MA

Abstract: The lateral prefrontal (LPFC) and the anterior cingulate (ACC) cortices play crucial roles in working memory. However, the specific cytoarchitectonic areas, circuits, and cell types engaged during task performance, and how these are altered in aging, remain poorly understood in the primate brain. To identify task-activated inhibitory neurons (InN) across prefrontal subareas, we quantified immediate early gene c-Fos expression in defined interneuron subclasses 3 hours after performance of the delayed recognition span task-spatial (DRSTsp), a test of spatial working memory, in young (n=3) and aged (n=3) rhesus macaques. We used immunohistochemistry to co-label c-Fos+ cells and markers for three non-overlapping subtypes of GABAergic InNs expressing calcium-binding proteins (CaBPs): calbindin-D28K (CB), calretinin (CR), and parvalbumin (PV) in LPFC (areas 9, 12, and 46) and ACC (areas 24 and 32). We analyzed the regional and laminar distribution of InNs that also expressed c-Fos, and thus, are presumably task-activated. The overall numbers of InN subtypes did not significantly differ between young and aged monkeys. Among all InN subtypes, c-Fos+/PV+ cells were the rarest subgroup across all cortical areas relative to c-Fos+/CB+ cells and c-Fos+/CR+ cells in both young and aged monkeys. Further, the proportion of PV+/c-Fos+ cells was significantly higher in ACC than in LPFC (ANOVA: region x InN subtype, p=0.0067). The laminar depth of c-Fos+

inhibitory interneurons significantly differed by subclass, with PV+/c-Fos+ cells biased toward deeper layers 4-6 compared with CB+/c-Fos+ and CR+/c-Fos+ cells that were more prevalent in the upper cortical layers 1-3 (ANOVA: depth x InN subtype $p<0.05$). Interestingly, effects of age were found primarily on these laminar depth profiles that depended on cortical area. Compared to young monkeys, aged monkeys showed a significant shift in prevalence of cFos+ CB and CR InNs into the deeper layers in LPFC area 9, but towards more superficial layers of LPFC area 46d and dorsal ACC area 24c ($p<0.05$). Overall, these findings demonstrate region-, layer-, and subtype-specific recruitment of inhibitory interneurons in ACC and LPFC during spatial working memory, and suggest that aging alters the engagement of inhibitory circuits across prefrontal areas.

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Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.15/KK27

Topic: I.03. Decision Making

Title: PUPIL RESPONSE REFLECTS THE PREDICTED COGNITIVE LOAD OF DIFFERENT REASONING STRATEGIES

Authors: *M. ZAMBRE[1], W. R. STAUFFER[2];
[2]Neurobio., [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: A hallmark of primate cognition is the ability to carry out slow, deliberative reasoning to solve complex problems, even ones we have never seen before. For example, home buyers carefully reason through budgets, neighborhood preferences, and property details to arrive at a final purchasing decision. In contrast, real-estate agents develop expertise through repeated experiences that allow them to quickly identify good home deals from property details, forming intuition through practice. This effortful/automatic divide in problem-solving has formed the foundation of many cognitive theories, but the neurophysiological mechanisms driving them have not been studied, because we lacked a behavioral paradigm that could readily generate both modes of cognition.We previously developed a novel rhesus macaque behavioral paradigm inspired by the knapsack problem - a combinatorial optimization problem widely used in computational complexity theory. Our “knapsack task” presents the animal with five items, otherwise known as an “instance” of the knapsack problem. Each item is associated with a specific juice amount, for example, 0.45 ml. The animal can select any combination of items; if the sum of the selected combination does not exceed 0.8 ml, the animal receives a reward equal to the sum of the combination. Selected combinations that exceed 0.8 ml result in no reward. We have previously shown that monkeys’ solutions reflected the output of deterministic algorithms, and this result established the behavioral paradigm for studying the neural basis of algorithmic

reasoning. Here, we optimized the knapsack task for measuring pupil diameter changes, and overtrained certain instances to enable automatic solution retrieval on those instances.Our preliminary behavioral data indicate that pupil diameter reflects the cognitive load predicted by the algorithm the animal uses to solve the knapsack task. Pupil diameter measurements show greater dilation when the animal approximated high-complexity reasoning processes that consider combinations, compared to when the animal used low-complexity approaches that operated one item at a time. Pupil diameter was even further reduced when the animal retrieved learned solutions. These results are consistent with the effortful/automatic divide in cognitive processing and validate our approach. In the future, we will introduce two stimulus sets, one novel and one well-learned, and record how neural systems adapt to different modes of reasoning.

Disclosures: M. Zambre: None. **W.R. Stauffer:** None.

Poster

PSTR285: Prefrontal Cortex and Decision-Making

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR285.16/KK28

Topic: I.03. Decision Making

Support: NIH R01MH128669
NIH DP2MH113095

Title: Algorithmic reasoning correlates in prefrontal neurons

Authors: *T. HONG[1], W. R. STAUFFER[2];
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Abstract: Complex economic decisions are often combinatorial: they require individuals to select from many alternatives under strict constraints on time, resources, and energy. As the number (n) of alternatives increases, the number of potential solutions grows exponentially (2^n) - a relationship that results in combinatorial explosion. To manage this computational complexity, we use algorithms - planned, structured sequences of computations - to efficiently approximate the optimal solutions. Despite the ubiquity of combinatorial problems, we do not know what algorithms are used nor how they are implemented in the brain. Using a combinatorial optimization paradigm, we show that the animals track the combinatorial upper bound—the best achievable outcome given the options examined so far. We recorded single neurons in the dorsolateral prefrontal cortex (DLPFC). A subset of DLPFC neurons produced phasic responses when the upper bound improved. These responses reflected the magnitude of the improvements, and were not explained by item value, local value comparisons, visual feedback, nor eye movements. Rather, these 'Bound-update neurons' signaled online, combinatorial computations. A distinct subset of ramping DLPFC neurons encoded the level of the upper bound itself. The rate at which their activity ramped reflected the rate at which the upper bound increased.

Moreover, variability in 'Upper-bound' neuron activity was correlated with performance on a trial-by-trial basis. In order to identify the algorithms DLPFC implements, we exploited the fact that different algorithms produce different running estimates - or incumbents - of the theoretical upper bound. For example, a greedy algorithm tracks only the largest item scanned so far whereas beam search maintains the top-k partial sums after each scan and discards the rest. These implementation differences cause each algorithm's incumbent trajectory to deviate from the upper bound in characteristic ways. We trained linear decoders on pseudopopulation activity to predict whether each algorithm's incumbent increased during epochs of upper-bound improvement. We compared both hill-climbing algorithms that maintain a single combination and combinatorial algorithms that maintain multiple candidates in parallel. Decoder performance was consistently higher for combinatorial algorithms than for hill-climbing algorithms, indicating that DLPFC tracks not just the current best solution, but multiple candidate combinations held in parallel. We have begun high-density population recordings to examine the neurobiological implementation of reasoning algorithms.

Disclosures: T. Hong: None. **W.R. Stauffer:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.01/KK29

Topic: I.06. Social Cognition

Support: Raynor Cerebellum Project
NIH Grant R21MH140296

Title: Electric field intensity predicts change in social cognition performance after cathodal cerebellar tDCS in neurotypical and autistic young adults

Authors: *M. M. LEE[1], J.-H. KIM[1], J. DUST[2], R. TEGIACCHI[2], A. SCHWARTZ[2], C. J. STOODLEY[1,2];
[1]Developing Brain Inst., Children's Natl. Hosp., Washington, DC; [2]American Univ., Washington, DC

Abstract: Results from tDCS studies frequently indicate mixed behavioral outcomes across individuals, i.e., some show improved performance while others may worsen or show no changes in response to tDCS. The factors that determine whether an individual is a tDCS responder (either positively or negatively) or a non-responder are currently unclear, though some theories suggest individual anatomical properties (skull, CSF, neural tissue) are promising candidates for predicting individual response. Here, we examined the relationship between individualized electric field (EF) estimates and change in behavior after tDCS. The current study included 11 neurotypical (NT) young adults (M = 22.5 yrs, SD = 3.4 yrs, 18-30 yrs, 8 females) and 8 age- and cognition-matched young adults diagnosed with autism (AS; M = 22.4 yrs, SD = 5.0 yrs, 19-

34 yrs, 3 females). All participants completed three study sessions which included 20min of 1.5mA of tDCS (anodal, cathodal, and sham) targeting the right posterolateral cerebellum followed by completing Reading the Mind in the Eyes (RME) task, a social cognition task in which participants infer the emotion portrayed in an image of just the eye region. T1-weighted MRI images from each participant were used to model the average cerebellar EF intensity in the posterolateral cerebellum (right lobules VI-IX). Linear mixed effects models indicated an interaction between EF intensity and cathodal tDCS for RME accuracy ($p = 0.027$, FDR corrected) and efficiency ($p = 0.045$, FDR corrected), indicating that higher EF in the cerebellum was associated with better RME accuracy and efficiency scores after cathodal tDCS compared to sham tDCS. There were no statistically significant effects of group (NT, AS) or anodal tDCS. Here, we provide evidence that EF intensity at the neural tissue may be a significant predictor of tDCS response. Results have implications for the interpretation of prior tDCS literature and the design of future studies. EF modeling using individual anatomical characteristics should be incorporated to determine optimal electrode placement and intensity for each subject (i.e., individualized tDCS rather than "one size fits all") to achieve sufficient EF intensity at the targeted neural tissue to induce behavioral change.

Disclosures: M.M. Lee: None. **J. Kim:** None. **J. Dust:** None. **R. Tegiacchi:** None. **A. Schwartz:** None. **C.J. Stoodley:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.02/KK30

Topic: I.06. Social Cognition

Support: R15MH106957
R15MH126404
DoD W81XWH-19-1-0249

Title: Midline cerebellar modulation improves social learning in autistic adults

Authors: *J. DUST[1], R. F. TEGIACCHI[2], A. SCHWARTZ[3], M. PAKNEJAD[2], C. J. STOODLEY[4];
[1]Neurosci., [2]American Univ., Washington, DC; [4]Neurosci., [3]Children's Natl. Med. Ctr., Washington, DC

Abstract: Challenges in social interaction are a hallmark feature of autism, yet the underlying neural mechanisms are unclear. Atypical cerebellar structure and function are consistently implicated in autism, particularly the posterior midline and right lateral cerebellum. Preclinical mouse models suggest that while inhibition of the posterior midline and right lateral cerebellum worsened social behavior, only right lateral stimulation rescued social impairment. Here, we extend this design to autistic (AUT) and neurotypical (NT) humans using cerebellar transcranial

direct current stimulation (tDCS), functional MRI and during a social learning task (Cyberball), with potential for clinical utility. We hypothesized that (1) the AUT cohort would show less social learning and reduced cerebellar activation during the learning stages of the task vs NT, (2) right lateral tDCS would improve social learning and increase activation in associated brain regions compared to baseline. Forty-three NT and 29 AUT adults received either posterior midline (n=25) or right lateral (n=47) cerebellar tDCS during 3 MRI sessions, with tDCS condition (anodal=excitatory, cathodal=inhibitory, or sham=baseline) pseudorandomized across sessions. Cyberball is a social learning task where participants toss a ball with three fictitious players whose toss probabilities are experimentally controlled. "Good," "neutral," and "bad" players emerge across stages based on how often the participant's tosses were returned. As the goal is to receive as many tosses as possible, learning is demonstrated by an increasing number of tosses to the good player over the task stages (early, late). ANCOVAs showed similar task performance between groups at baseline. Linear mixed models revealed that midline modulation improved early learning performance in the AUT cohort relative to sham (anodal $p=0.040$; cathodal $p=0.006$), supported by neuroimaging data showing midline cathodal modulation increased activation in right lateral cerebellum during learning ($p<0.005$, $k>20$). Midline cathodal tDCS also improved overall social learning in AUT relative to sham ($p=0.045$). Right lateral anodal modulation worsened whole-task performance in the entire cohort relative to sham ($p=0.040$). Contrary to preclinical findings, midline rather than right lateral cerebellar modulation improved social learning in the AUT cohort. However, neuroimaging findings show increased right lateral activation after midline inhibition, suggesting a potential shared mechanism between these regions. These results support cerebellar modulation as a potential clinical intervention for social learning in autistic adults.

Disclosures: J. Dust: None. **R.F. Tegiacchi:** None. **A. Schwartz:** None. **M. Paknejad:** None. **C.J. Stoodley:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.03/KK31

Topic: I.06. Social Cognition

Title: Neurovisual Signatures of Social Attention Across Autism, ADHD, and Typical Development

Authors: *J. LIMA DO ESPIRITO SANTO[1], L. AZAMBUJA[2];
[1]Private Practice, Estrela, Brazil; [2]Private Practice, Porto Alegre, Brazil

Abstract: Altered social attention is one of the most consistently reported findings in Autism Spectrum Disorder (ASD), particularly reduced visual attention to socially relevant facial regions. Although eye-tracking studies have contributed substantially to understanding these patterns, most systems require specialized equipment, limiting their use in routine clinical

practice. This study investigated whether a webcam-based eye-tracking platform could identify differences in visual attention among children with ASD, Attention-Deficit/Hyperactivity Disorder (ADHD), and Typical Development (TD) during a neuropsychological assessment protocol. Participants included 72 children previously classified through clinical and neuropsychological evaluation as ASD Level 1-2 (n = 25), ADHD (n = 21), or TD (n = 26). Children viewed a standardized set of visual stimuli, including facial photographs, classroom scenes, playground scenes, and social interaction scenes. Gaze coordinates were collected through a webcam-based eye-tracking system and analyzed using predefined Areas of Interest (AOIs). Across facial stimuli, children with typical development allocated a greater proportion of visual attention to the eye region than children with ASD. In one representative facial stimulus, mean fixation on the eyes was 27.5% in the TD group, 19.9% in the ADHD group, and 16.0% in the ASD group. Children with ASD also directed a larger proportion of gaze outside predefined facial AOIs. Heatmap and scanpath analyses revealed broader visual exploration patterns and reduced concentration on socially relevant facial regions in the ASD group. Children with ADHD generally demonstrated intermediate patterns, with gaze allocation more closely resembling TD participants than those with ASD. Considerable variability was observed within each group, reflecting the heterogeneity commonly seen in neurodevelopmental conditions. Nevertheless, the overall pattern of findings was consistent with previous eye-tracking studies reporting reduced attention to socially relevant facial features and greater gaze dispersion in autism. These findings indicate that webcam-based eye tracking can capture meaningful differences in social visual attention among children with ASD, ADHD, and typical development. The results support the use of accessible digital technologies as complementary tools for investigating social attention in pediatric neurodevelopmental populations.

Disclosures: J. Lima do Espirito Santo: None. **L. Azambuja:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.04/KK32

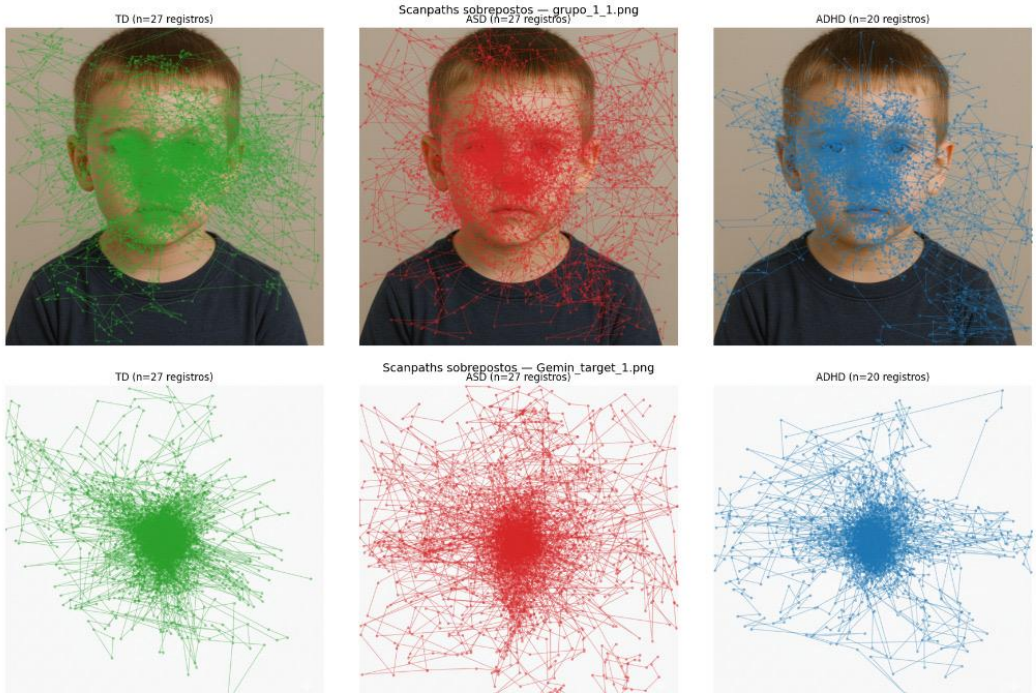
Topic: I.06. Social Cognition

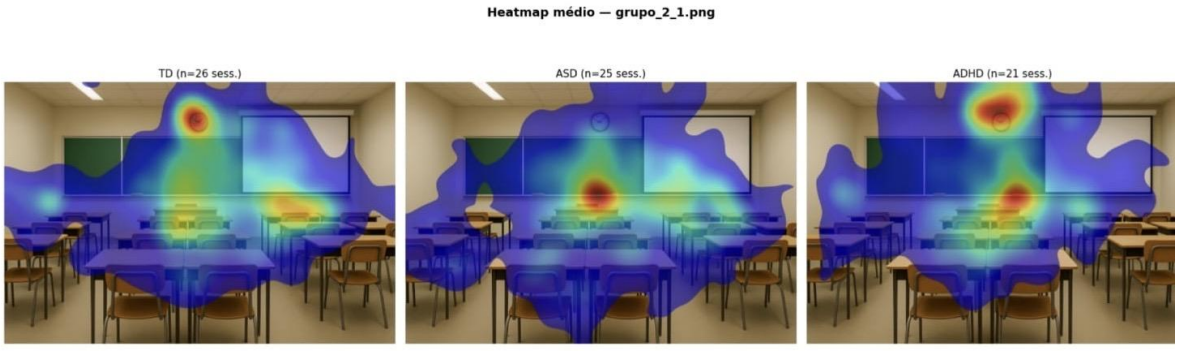
Title: Distinct Digital Gaze Signatures in Autism and ADHD Revealed by Low-Cost Webcam Eye Tracking

Authors: *L. AZAMBUJA[1], J. LIMA DO ESPIRITO SANTO[2];
[1]Private Practice, Porto Alegre, Brazil; [2]Private Practice, Estrela, Brazil

Abstract: Background: Eye-tracking studies have identified atypical social attention patterns in autism spectrum disorder (ASD), but widespread implementation remains limited by the cost of specialized equipment. We investigated whether a low-cost webcam-based eye-tracking platform could detect distinct visual exploration patterns across neurodevelopmental groups. Methods: 72 children and adolescents (TD, n=26; ASD, n=25; ADHD, n=21) completed a brief eye-tracking

protocol. Stimuli included facial images and ecologically valid social scenes. Group-level heatmaps and overlaid scanpaths were generated from gaze coordinates obtained through standard webcam recordings. Results: Distinct gaze signatures emerged across groups. TD participants showed greater attentional convergence toward socially relevant regions and more concentrated visual exploration patterns. ASD participants demonstrated broader gaze dispersion and reduced convergence toward common social targets. ADHD participants displayed an intermediate profile, maintaining attention to salient regions while exhibiting greater exploratory behavior. Similar patterns were observed across facial and classroom-based social stimuli. Conclusions: Low-cost webcam-based eye tracking identified distinct visual exploration signatures associated with ASD and ADHD. Heatmap and scanpath analyses may provide scalable digital biomarkers for neurodevelopmental assessment, research, and population-level screening.





Disclosures: L. Azambuja: None. **J. Lima do Espirito Santo:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.05/KK33

Topic: I.06. Social Cognition

Support: NIH K Award, K99HD118079

Title: Neural Correlates of Intervention-Related Social Cognitive Improvement in Autistic Adults

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[1]The Univ. of Texas Hlth. Sci. Ctr. at Houston, Dept. of Psychiatry and Behavioral Sc, Houston, TX; [2]Univ. of MD Baltimore, Baltimore, MD; [3]Maryland Psychiatric Res. Ctr., Baltimore, MD

Abstract: Autistic adults often face unique challenges during transitions to independence. The ¡Iniciando! la Adultez therapy program is a culturally-adapted, evidence-based therapy program for autistic adults transitioning to adulthood, focused on providing skills for social cognition. This exploratory study, supported by an NIH K99 award (K99HD118079), investigated the neural mechanisms underlying social cognitive changes following this targeted intervention. Autistic human adults (N=28; after rigorous quality control) completed a longitudinal fMRI study consisting of baseline and post-intervention scans. Participants were divided into Treatment and Control groups. During scanning, participants performed a social cognition task contrasting emotional processing with general baseline conditions. Data were preprocessed using a standard nonlinear alignment pipeline to the MNI template. To ensure rigorous statistical modeling, baseline head motion (Euclidean norm) was included as a voxel-wise covariate in our mixed-effects longitudinal models. Whole-brain group analyses were rigorously corrected for family-wise error (FWE) using spatial autocorrelation Monte Carlo simulations. At baseline, before any intervention, we observed robust, significant main effects for the social cognition task across the entire cohort. Even after strictly controlling for baseline head motion, the social cognition condition elicited widespread significant activation, validating the experimental paradigm. The largest significant cluster of activation for this baseline task effect was located in the area corresponding to the anterior middle temporal gyrus within the lateral temporal cortex. This region survived strict FWE correction limits (voxel-wise uncorrected $p < 0.001$, spatial autocorrelation alpha = 0.05, nearest-neighbor level 2 minimum cluster extent $k = 19$ voxels). Longitudinally, comparing baseline and follow-up scans, we isolated significant condition-by-time neural changes. While the Control group, which did not receive the targeted intervention, exhibited no significant neural changes, the Treatment group demonstrated distinct, statistically significant alterations in regional activation during the Social Cognition condition that survived FWE thresholding. These available data suggest that the intervention successfully modulates neural networks associated with social processing in autistic adults. The robust baseline findings

confirm the task's validity, while the longitudinal group differences provide biological evidence that the therapy program can drive functional neural plasticity in autistic young adults.

Disclosures: A.F. Pagan: None. **P. Kochunov:** None. **E. Hong:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.06/KK34

Topic: I.06. Social Cognition

Support: the General Insurance Association of Japan
Inogashira Hospital Grants for Psychiatry Research
the Japanese Society for Higher Brain Dysfunction
JSPS KAKENHI Grant Number 24K02374
the Ministry of Health, Labour and Welfare (Health Labour Sciences Research Grants 20GC1018 and 22GC1004)

Title: Preserved Moral Judgment but Slower Moral Decision-Making in Acquired Brain Damage

Authors: *M. SUGANAMI[1,3], K. TAKAHATA[4], Y. MIMURA[2], M. YAMAMOTO[5], T. MURAMATSU[2], M. MIMURA[6];
[1]Dept. of Neuropsychiatry, Keio Univ. Sch. of Med., Tokyo, Japan; [2]Dept. of Neuropsychiatry, Keio Univ. Sch. of Med., Shinjuku, Japan; [3]Dept. of Rehabil., Kuromegawa Clin. Asakadai, Med. Corp. Gorinkai, Asaka, Japan; [4]Advanced Neuroimaging Ctr., Natl. Inst. for Quantum Sci. and Technol. (QST), Chiba, Japan; [5]Yokohama Brain and Spine Ctr., Yokohama, Japan; [6]Ctr. for Preventive Med., Keio Univ., Tokyo, Japan

Abstract: Background
Moral judgment is thought to depend on emotional and executive processes. Previous work showed that individuals with acquired brain damage (ABD) exhibit reduced coupling between emotional arousal and moral judgments, suggesting altered integration of emotional information. However, it remains unclear whether moral judgment outcomes and the cognitive processes required to reach them are affected by the same mechanisms.
Methods
Thirty-five individuals with acquired brain damage (ABD) and thirty healthy controls (HC) completed a moral judgment task consisting of five scenario types: Responsibility (R), Diminished Responsibility (DR), Mitigating Circumstances (MC), Violation of Norms (VN), and No Consequence (NC).Participants rated wrongness and emotional arousal. Emotion-Judgment Coupling (β) was calculated as an index of the extent to which emotional arousal influenced moral judgments. Reaction time (RT) was also recorded.Executive function was assessed using the Frontal Assessment Battery (FAB) and Trail Making Test (TMT).
Results

ABD participants showed significantly reduced Emotion-Judgment Coupling compared with healthy controls ($\beta = 0.51$ vs. 0.74, $p = .045$).ABD participants also required longer reaction times across conditions. Significant group differences were observed in the Responsibility condition (10.33 vs. 3.31 s, $p = .006$) and Diminished Responsibility condition (13.55 vs. 6.07 s, $p = .003$).Reaction time was not associated with Emotion-Judgment Coupling ($r = -0.16$, $p = .216$).However, longer reaction times were associated with poorer executive function, as measured by TMT-A ($r = .44$, $p = .002$), TMT-B ($r = .50$, $p < .001$), and FAB scores ($r = -.42$, $p = .006$).Executive function measures were associated with reaction time but not with final moral judgment ratings.

Conclusions

The present findings suggest a dissociation between moral judgment outcomes and the cognitive processes underlying moral decision-making following acquired brain damage.Reduced Emotion-Judgment Coupling appears to influence the content of moral judgments, whereas prolonged decision times are more strongly associated with executive dysfunction.These findings suggest that moral knowledge and judgment outcomes may remain relatively preserved after brain damage, while greater executive resources are required to integrate information and arrive at moral decisions.

These findings suggest that executive dysfunction primarily affects the efficiency of moral decision-making rather than the moral evaluations themselves.

Disclosures: M. Suganami: None. **K. Takahata:** None. **Y. Mimura:** None. **M. Yamamoto:** None. **T. Muramatsu:** None. **M. Mimura:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.07/KK35

Topic: I.06. Social Cognition

Support: NIMH R01MH131637
Florida International University Center for Children and Families Seed Funding grant

Title: Does the type of social observation matter? Examining error monitoring and social anxiety symptom domains under distinct forms of social observation

Authors: *O. A. STIBOLT, G. A. BUZZELL;
Psychology, Florida Intl. Univ., Miami, FL

Abstract: For individuals with social anxiety (SA), making mistakes in front of others can feel especially significant. The brain detects mistakes via error monitoring, which is commonly indexed by the error-related negativity (ERN), a neural signal detectable in scalp-recorded electroencephalography (EEG). Prior work demonstrates that the ERN is typically enhanced

while under social observation. However, most studies examining the effect of social observation on the ERN employ paradigms that utilize a combination of two types of observation: observation of the accuracy/speed of the participant and observation of the participant's body/face during a task. Prior work has not sought to isolate the effects of these distinct forms of social observation on the ERN. Moreover, it remains unknown whether the effects of distinct forms of social observation map onto distinct symptom domains of SA (specifically fear of negative evaluation and fear of physical symptoms). In the present study, 94 participants aged 18-59 completed a flanker task under three conditions: alone, task-focused observation (TFO), and personal observation (PO). In TFO, an observer watched the participant's accuracy and speed via the participant's screen and a secondary monitor that displayed trial-level feedback. In PO, the observer watched the participant themselves via a direct view and live webcam footage of the participant's face on a secondary monitor. Participants reported their fear of negative evaluation with the Brief Fear of Negative Evaluation (BFNE) Scale and their fear of physical symptoms with the Social Concerns subscale of the Anxiety Sensitivity Index 3 (ASI-3). Contrary to our hypotheses, we did not replicate the effect of social observation on the ERN. There were no significant differences in the ERN between the alone condition and either TFO or PO, nor was there a distinction between the two social conditions. Furthermore, levels of fear of negative evaluation and fear of physical symptoms did not significantly influence relations between the social observation condition and the ERN. One possibility is that the integration of multiple observation methods (within the same condition) is necessary to elicit previously observed effects of social context on the ERN, but further research is needed.

Disclosures: O.A. Stibolt: None. **G.A. Buzzell:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.08/Web Only

Topic: I.06. Social Cognition

Title: Social cognition interventions for adults with mood disorders and suicidality

Authors: *M. MURILLO RAMIREZ;
Fac. of Social Sci. and Humanities, Univ. Nacional Abierta y a Distancia - UNAD, Medellín, Colombia

Abstract: Suicide is a global public health concern, and adults with mood disorders exhibit an increased risk. These behaviors have been associated with deficits in social cognition (SC). Objective: To synthesize literature on SC interventions for adults with mood disorders and suicidality risk. Methods: A systematic search was conducted across PubMed, Scopus, Cochrane Library, ScienceDirect, and Embase databases for publications in English and Spanish from 2013 to 2023. The methodological quality of the selected articles, the characteristics of the interventions, and their effects on suicidality were evaluated. Results: Five articles met the

eligibility criteria, comprising 1,508 participants aged 18-65 years. The findings highlight the potential of SC interventions for this population. However, the scarcity of interventions utilizing this approach and the methodological variability across studies limited a comprehensive comparison of the results. Conclusion: These findings provide evidence to support decision-makers in diverse healthcare settings to mitigate suicide risk. Future research should establish standardized measurement protocols to facilitate comparison between interventions.

Disclosures: M. Murillo Ramirez: None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.09/KK36

Topic: I.06. Social Cognition

Support: R0l MH119430
R01MH103831
Gustavus and Louise Pfeiffer Research Foundation
state of Connecticut Department of Mental Health and Addiction Services

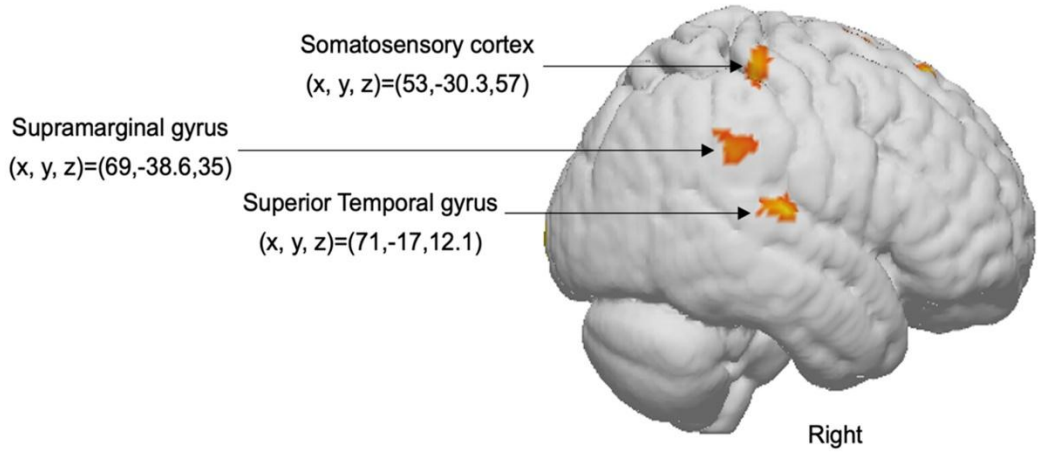
Title: A multimodal approach to identify atypical face processing systems in schizophrenia

Authors: *D. PURUSHOTHAMAN[1], J. A. NOAH[2], X. ZHANG[2], R. SINGH[4], C. TEK[2], V. SRIHARI[2], J. HIRSCH[3];
[1]Psychiatry, Yale Univ., New Haven, CT, USA, CT; [2]Psychiatry, Yale Sch. of Med., New Haven, CT; [3]Dept. of Psychiatry, Yale Sch. of Med., New Haven, NY; [4]Electrical Computer and Biomed. Engin., Univ. of Rhode Island, Kingston, RI

Abstract: Introduction: Social interaction difficulties are common in schizophrenia. Identifying the neural underpinnings of social symptomatology could reveal candidate targets for neuromodulation. As a first step, we aimed to isolate atypical neural systems associated with live social interaction in first episode psychosis ,FEP, (within 3 years of onset of a schizophrenia spectrum disorder). **Methods:** A two-person live face gaze paradigm was employed as the behavioral proxy for social interaction. Electroencephalography (EEG), functional near infrared spectroscopy (fNIRS), eye tracking, and facial movement measures were simultaneously acquired[1,2] from 32 typically developed(TD) and 24 FEP participants. We hypothesized that these measures would isolate atypical social neural systems in FEP. **Results:** Involuntary behavioral responses (live facial mimicry and gaze fixation) were reduced in FEP. Event Related Potential (ERP) amplitudes and latencies were atypical in FEP during the first 100-300 ms. Power spectra decomposition showed reduced theta oscillations localized to the right temporoparietal region, consistent with atypical oscillatory rhythms in the face processing circuit. In addition, fNIRS data showed reduced hemodynamic activity in the right temporoparietal region during live face gaze (Fig 1: right supramarginal gyrus [$p \leq 0.02$], right

superior temporal gyrus[p≤0.01], right somatosensory cortex[p≤0.01])[3]. **Conclusions:** These findings suggest that live face processing systems are atypical in early schizophrenia spectrum disorder, and provide an evidence-based framework to hypothesize candidate targets for neuromodulation.1 Hirsch, J. et al. Neural mechanisms for emotional contagion and spontaneous mimicry of live facial expressions. *Philos Trans R Soc Lond B Biol Sci* (2023)2 Singh, R. *et al.* Deep multimodal representations and classification of first-episode psychosis via live face processing. *Front Psychiatry* (2025)3 Purushothaman,D. et al. A multimodal approach to identify atypical face processing systems in schizophrenia *(Submitted)*

Figure 1:Hypoactive live face encoding regions in early schizophrenia



Disclosures: D. Purushothaman: None. **J.A. Noah:** None. **X. Zhang:** None. **R. Singh:** None. **C. Tek:** None. **V. Srihari:** None. **J. Hirsch:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.10/KK37

Topic: I.06. Social Cognition

Support: Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI) [EAM-833490]
Sistema de Registro y Evaluación de la Investigación (SIREI) [TCLL-43200202477]
Sistema Nacional de Investigadoras e Investigadores (SNI) [TCLL-210785]

Title: Internalizing symptoms and psychosocial risk are differentially associated with social cognition in adolescents

Authors: *L. CASTAÑEDA LANDA[1,2], S. ZAMORA LUGO[3,4], L. HERNANDEZ SALAZAR[2], J. FERNANDEZ-RUIZ[5], T. CIBRIAN-LLANDERAL[2,4];
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Abstract: Adolescence is a period of neurobiological, emotional, and social reorganization in which interpersonal demands increase and the ability to interpret social cues becomes especially relevant. In this context, anxiety, depression, and psychosocial risk may be associated with different components of social cognition. This study examined the relationship between mental health indicators, psychosocial risk, and social cognition in school-aged adolescents. Participants were 447 adolescents from public high schools in Xalapa, Veracruz, Mexico, aged 14 to 19 years (M = 16.04, SD = 0.96; 188 females, 259 males). Anxiety was assessed with the Beck Anxiety Inventory (BAI), depression with the Beck Depression Inventory-II (BDI-II), and psychosocial risk with the Problem Oriented Screening Instrument for Teenagers (POSIT). Social cognition was assessed through self-reported empathy (EQ-10), mental-state decoding from the eye region (Reading the Mind in the Eyes Test, RMET), and complex facial emotion recognition (Cambridge Mindreading Test, CAM). Separate hierarchical linear regressions were conducted for each dependent variable, entering sex and age in block 1, anxiety and depression in block 2, and either global psychosocial risk or POSIT subscales in block 3. In the model including global risk, empathy shows the largest explained variance (R^2 = .105). Age (β = .230, p < .001), depression (β = .142, p = .005), and global psychosocial risk (β = .191, p < .001) positively predicts empathy, whereas anxiety shows a marginal negative association (β = −.135, p = .022). In contrast, the models for RMET and CAM explain less variance (R^2 = .028 and R^2 = .015, respectively), and global psychosocial risk does not predict performance. When POSIT subscales were entered, the models explained 12.1% of the variance in empathy, 6.2% in RMET, and 5.1% in CAM. Family relationship risk is negatively associated with RMET performance (β = −.226, p = .025), whereas educational risk is the strongest negative predictor of CAM performance (β = −.270, p < .001). These findings suggest that social cognition in adolescence does not behave as a unitary process; empathy is mainly related to age, depressive symptoms, and global psychosocial risk, whereas performance-based tasks appear to be associated with specific contextual risk domains.

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Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.11/KK38

Topic: H.04. Emotion

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Title: Medial infant frontal alpha asymmetry patterns during maternal disengagement relate to bifactor-derived maternal internalizing symptoms

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Abstract: Maternal depression and anxiety are associated with infant socio-emotional development, but it remains unclear how shared maternal internalizing symptoms relate to infants' dynamic neural responses to maternal disengagement. Frontal alpha asymmetry (FAA) indexes relative frontal activity linked to approach-withdrawal motivation and emotion regulation, with more positive FAA commonly interpreted as approach-related regulation and more negative FAA as withdrawal-related responses. We examined whether medial and lateral FAA trajectories during the Still-Face Paradigm (SFP) were associated with a general maternal internalizing factor derived from item-level depression and anxiety symptoms. High-density EEG was recorded from 6-month-old infants (N=33; 16F/17M) from a Singaporean cohort during four 30-s SFP episodes: happy interaction, maternal phone disengagement, reunion, and still-face. FAA was calculated in the 6-9 Hz infant alpha band as ln(right alpha power)-ln(left alpha power), separately for medial and lateral frontal regions. Exploratory K-means clustering (k=2) was performed on FAA trajectories across SFP episodes. To obtain a unified maternal mental health index, we conducted exploratory bifactor analysis using the 6-month EPDS and STAI item-level data from the wider cohort (N=830 complete cases). Items were reverse-coded so higher scores reflected greater symptom severity. The general bifactor dimension showed positive loadings across EPDS and STAI items and was interpreted as a general maternal internalizing factor. For medial FAA, clustering identified two separable trajectory phenotypes (silhouette=0.46, permutation p=0.016). Cluster 1 showed overall positive medial FAA and partial rebound during reunion following maternal phone disengagement, whereas Cluster 2 showed overall negative medial FAA without comparable rebound. Among infants with available bifactor scores (N=28), medial clusters differed in general maternal internalizing scores: Cluster 1 showed lower scores (n=12, M=-0.71, SD=0.68) than Cluster 2 (n=16, M=0.15, SD=1.19), Welch t(24.54)=-2.41, p=0.024. Lateral FAA also showed separable trajectory profiles (silhouette=0.51, permutation p=0.001), but clusters did not differ in maternal internalizing scores, Welch t(22.29)=0.04, p=0.969. These exploratory findings suggest that medial, but not lateral, infant FAA trajectories during maternal disengagement may be sensitive to general maternal depression/anxiety symptom burden. Item-level bifactor modelling may provide a parsimonious way to capture shared maternal internalizing symptoms and relate them to infant neural regulation.

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Poster

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Program #/Poster #: PSTR286.12/KK39

Topic: I.06. Social Cognition

Support: SECIHTI CVU-1087378
SIREI (TCLL-43200202477)
SNI (TCLL-210785)

Title: Intranasal Oxytocin Modulates Social Cognitive Performance as a Function of Sex and Internalizing Symptoms: A Double-Blind Placebo-Controlled Study

Authors: *L. L. CRUZ ZAVALETA[1], R. TRIANA-DEL RIO[4], J. FERNANDEZ-RUIZ[5], G. A. CORIA-AVILA[2], T. CIBRIAN-LLANDERAL[3,6];
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Abstract: Background: Intranasal oxytocin has been proposed as a pharmacological intervention to enhance social cognition, although findings remain inconsistent, potentially due to insufficient consideration of biological sex and individual variability in social cognitive functioning.Objectives: To characterize social cognitive variability as a function of sex and internalizing symptoms (Study 1), evaluate acute effects of intranasal oxytocin (24 IU) in a three-arm randomized controlled trial (Study 2), and explore whether social cognitive performance predicts treatment response.Methods: Study 1 included 156 healthy adults. Study 2 was a parallel-group randomized controlled trial with oxytocin (n=30), placebo (n=30), and no-intervention control (n=30), balanced for sex (15M/15F per group). Outcomes included IRI subscales and RMET scores. Analyses comprised factorial ANOVA with Benjamini-Hochberg correction, Bayesian t-tests, Spearman correlations, K-means clustering, individual treatment effect estimation, and leave-one-out cross-validated (LOOCV) logistic regression.Results: Oxytocin significantly enhanced Empathic Concern (Hedges g=0.76, pBonferroni=0.012, BF10=5.39) and recognition of negative emotions (g=0.75, p=0.014, BF10=4.81). Sex moderated response magnitude: males exhibited broad effects on the Global Social Cognition composite (g=1.08, p=0.005, BF10=5.54, NNT=3.0), whereas females showed selective effects on Empathic Concern and negative emotion recognition. Oxytocin produced an anxiety-affective empathy coupling absent in placebo and control groups while eliminating the anxiety-theory-of-mind coupling observed under placebo. A logistic regression model based on cognitive variables showed high apparent predictive performance under LOOCV (90.0% accuracy; AUC=0.987), compared with 13.3% for a clinical-only model (sex, BAI, BDI). K-means clustering identified high- and low-social-cognition phenotypes with differential response to oxytocin (Cohen's d=1.57, p=0.0005).Conclusions: Intranasal oxytocin modulated affective empathy and negative emotion recognition. Individual variability in social cognitive performance was associated with

treatment response. Brief RMET and IRI assessments may provide a feasible approach for socio-cognitive profiling. Findings are preliminary and require replication in independent samples and clinical populations. The no-intervention control group enabled identification of potential procedure-related effects, supporting the value of three-arm designs in oxytocin research.

Disclosures: L.L. Cruz Zavaleta: None. **R. Triana-Del Rio:** None. **J. Fernandez-Ruiz:** None. **G.A. Coria-Avila:** None. **T. Cibrian-Llanderal:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

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Topic: I.06. Social Cognition

Support: 999872
SECIHTI STM-931445
SIREI [TCLL-43200202477]
(SNI) [TCLL-210785].

Title: Executive functioning in informal caregivers of cancer patients: between-group differences and within-group predictors of cognitive performance

Authors: *S. TOLEDO-MESA[1,3], S. ZAMORA LUGO[2,4], L. HERNANDEZ SALAZAR[1], R. L. CASTILLO LÓPEZ[5], M. BARRADAS-MOCTEZUMA[6], T. CIBRIAN-LLANDERAL[1,4]; [1]Inst. de Neuroetologia, [2]Facultad de Psicología, Univ. Veracruzana, Xalapa, Mexico; [3]Ctr. Estatal de Cancerología "Dr. Miguel Dorantes Mesa", Xalapa, Mexico; [4]Escuela de Psicología, Univ. Anáhuac, Xalapa, Mexico; [5]Terapéutico Ctr. de Psicoterapia Especializada, Xalapa, Mexico; [6]Inst. de Investigaciones Cerebrales, Univ. Veracruzana,Instituto de Investigaciones Cerebrales, Xalapa, Mexico

Abstract: Introduction: Cancer is the third leading cause of death in Mexico, and more than 70% of cases are diagnosed at advanced stages. This situation generates a significant burden for informal primary caregivers, who often assume caregiving responsibilities without prior training or financial compensation. The chronic stress associated with this role may affect prefrontal functioning, particularly executive processes such as working memory, inhibitory control, cognitive flexibility, and planning. **Method:** A cross-sectional, descriptive-comparative study was conducted with 76 women recruited at the State Cancer Center “Dr. Miguel Dorantes Mesa” (Xalapa, Veracruz) during 2024-2025. The sample included 54 informal primary caregivers of oncology patients and 22 healthy controls matched by age and education. Executive functioning was assessed using the BANFE-2 battery, which evaluates 15 cognitive processes across orbitomedial, anterior prefrontal, and dorsolateral regions. Perceived stress (PSS), caregiver strain (CSI), and caregiver burden (ZCB) were administered only to the caregiver group. Between-group differences were analyzed using Mann-Whitney U tests with FDR correction,

and diagnostic differences were examined using Kruskal-Wallis tests. Additionally, logistic regressions, ROC curves, and multiple linear regressions were performed. **Results:** Caregivers showed significantly lower scores than controls in the global Executive Functions score and in the dorsolateral region (adjusted ps < .05; r = .38 and .31, respectively). Significant differences were identified in 33 out of 45 subtests, with the largest effect sizes observed in semantic verbal fluency (r = .62), semantic classification (r = .57), and working memory (r = .52-.53). The most pronounced impairments were found in caregivers of patients with hematological and gynecological diagnoses. ROC analysis indicated that the global Executive Functions score was the best discriminator between groups (AUC = .743). None of the assessed stress variables significantly predicted executive performance within the caregiver group (R^2 = .010-.061). **Conclusions:** Informal primary caregivers of oncology patients exhibit measurable declines in executive functioning compared to women without caregiving roles. The lack of significant associations between stress and cognition suggests that the role itself may contribute more to cognitive differences than subjective stress indicators. The BANFE-2 may serve as a useful screening tool in occupational health. Longitudinal studies incorporating biological stress biomarkers are needed to clarify the underlying causal mechanisms.

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Poster

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Program #/Poster #: PSTR286.14/KK41

Topic: I.06. Social Cognition

Support: SECIHTI CVU 1087385
SIREI TCLL-43200202477
SNI TCLL-210785

Title: Cognitive and Affective Components of Theory of Mind and Suicidal Ideation in University Students: Differences Across Academic Areas

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Abstract: Theory of Mind (ToM) refers to the ability to infer one's own and others' mental states and comprises both cognitive and affective components. Although previous studies have

suggested a relationship between social cognition and suicidal behavior, findings remain inconsistent. This study examined the association between suicidal ideation and different ToM components across academic areas. A total of 185 university students participated. Measures included suicidal ideation, psychological functioning, and multiple ToM components, including facial emotion recognition, mental state inference, faux pas detection, and empathy. Correlational analyses focused on Health Sciences (n = 96) and Humanities (n = 35), the two academic areas with sufficient sample size for analysis. Cognitive ToM measures showed no significant associations with suicidal ideation or differences across academic areas. In contrast, affective ToM components displayed differential patterns. Among Humanities students, suicidal ideation was significantly correlated with facial emotion recognition ($\rho = -.375$, $p = .027$) and personal distress ($\rho = .486$, $p = .003$). Self-esteem also showed a stronger association with suicidal ideation in Humanities ($\rho = -.794$) than in Health Sciences students ($\rho = -.473$). Comparison of correlation coefficients using Fisher's z transformation indicated that both the association between personal distress and suicidal ideation ($z = -2.47$, $p = .013$) and the association between self-esteem and suicidal ideation ($z = 2.77$, $p = .006$) differed significantly between academic areas. These findings suggest that the relationship between suicidal ideation and psychological variables is not homogeneous across academic contexts. Whereas cognitive ToM components showed no relevant associations, an affective ToM component (personal distress) and a well-established psychological factor (self-esteem) demonstrated differential associations across academic areas. These findings highlight the importance of affective mentalizing processes and psychological factors in the neurocognitive study of suicidal ideation.

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Poster

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

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Topic: I.06. Social Cognition

Title: Hair cortisol is associated with negative affect and emotion dysregulation in graduate students: A psychobiological approach to academic stress

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Abstract: Academic stress in graduate students has been associated with negative affect and emotion dysregulation. However, few studies have integrated psychological measures with biomarkers of chronic stress. Hair cortisol concentration (HCC) provides an objective index of

long-term hypothalamic-pituitary-adrenal (HPA) axis activity.Sixty-nine graduate students from a public university in Mexico participated in this cross-sectional study. Academic stress was assessed using the SISCO-SV21, negative affect with the DASS-21, and emotion dysregulation with the DERS-15. Hair samples (3 cm) were collected from the posterior vertex region and cortisol concentrations were quantified by ELISA. HCC values were log10-transformed. Pearson correlations were used to examine associations between HCC and psychological variables.Most participants exhibited moderate academic stress (86%). Mean log-transformed HCC was 1.04 ± 0.43. HCC showed significant positive associations with academic stress symptoms ($r = 0.39$, $p = 0.001$), total academic stress scores ($r = 0.34$, $p = 0.002$), depression ($r = 0.37$, $p = 0.001$), stress ($r = 0.38$, $p = 0.001$), total negative affect ($r = 0.39$, $p < 0.001$), and total emotion dysregulation scores ($r = 0.35$, $p = 0.003$). Significant correlations were also observed with emotional clarity, goal-directed behavior, and emotional acceptance dimensions. Participants reporting lack of advisor support exhibited higher HCC levels ($p = 0.015$).These findings suggest that chronic physiological stress in graduate students is more closely related to negative affect and emotion dysregulation than to academic demands alone. Hair cortisol may represent a valuable biomarker for investigating psychobiological mechanisms underlying academic stress and emotional functioning in higher education settings.

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Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

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Topic: I.06. Social Cognition

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NICHD (R37 HD29957)
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Williams Syndrome Association (WSA 0104, WSA 0111)

Title: Morphometric Similarity MRI Identifies 7q11.23 Gene Dosage Effects on Neural Circuits Underlying Social Behavior

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Abstract: Background: Impairments in social functioning are prevalent in many idiopathic neuropsychiatric disorders such as autism and schizophrenia and can result in substantial debilitation. Efforts to identify neurogenetic mechanisms are complicated by clinical and genetic heterogeneity. Studying conditions in which the affected genes are known and the behaviors are well-defined substantially reduces the genetic search space. Copy number variants (CNVs) at chromosome 7q11.23 confer contrasts in social functioning: hemideletion causes Williams syndrome ([WS], with only one copy of ~26 genes), characterized by increased social drive and approach, whereas duplication (7q11.23 duplication syndrome, [Dup7], three copies of the same genes), is characterized by severe social anxiety and shyness. Here, we used Morphometric INverse Divergence (MIND), a multimodal structural similarity MRI approach sensitive to genetically-coordinated cortical organization, to identify circuit-level systems that exhibit 7q11.23 gene dosage effects. **Methods:** Structural T1-weighted MRI data were collected from 34 individuals with WS (12.0±4.0 years old), 21 people with Dup7 (14.1±2.9 years), and 112 age- and sex-matched typically developing participants (12.8±3.3 years). For each participant, Freesurfer generated surface-based measurements of five cortical features (volume, thickness, surface area, curvature, and sulcal depth) within the 68 cortical regions of the Desikan-Killiany anatomical atlas. MIND quantified similarity of the five feature distributions within regions using Kullback-Leibler divergence. General linear models tested for 7q11.23 gene dosage effects on regional MIND, controlling for age, sex, and Euler value, and results were thresholded at $p<0.05$, FDR-corrected. **Results:** Gene dosage effects were observed in 21 cortical regions. Regions associated with social perception and social motivation, including bilateral fusiform gyri, posterior cingulate regions, medial orbitofrontal cortex, right superior temporal gyrus, and right pars opercularis, showed less morphometric similarity, and thus greater specialization, in WS, but reduced specialization in Dup7. In contrast, regions associated with visuospatial abilities, including postcentral, paracentral, cuneus, right superior parietal, and parahippocampal regions, showed the opposite pattern. **Conclusions:** Reciprocal 7q11.23 CNVs result in opposite patterns of structural organization of cortical networks associated with social functioning. These findings identify circuit-level phenotypes linking gene-dosage to social/behavioral phenotypes.

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Poster

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Support: Genesis Grant
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Title: AI avatar-based psychiatric patient simulation engages social cognitive processes in nursing education: a pilot survey study

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Abstract: Effective psychiatric clinical education requires students to recognize and respond to complex emotional and behavioral presentations, yet traditional didactic methods offer limited opportunity for emotionally engaged, low-stakes clinical practice. Social cognitive and affective neuroscience proposes that observing emotionally expressive social agents activates processes underlying empathy, mentalizing, and emotion recognition — skills essential for psychiatric clinical communication. We developed generative AI avatars simulating patients presenting with depression (adjustment disorder, dysthymia, major depressive disorder), psychosis, and mania, with presenting features including low mood and chest tightness, using a localized ChatGPT-4 script pipeline and D-ID video synthesis to produce culturally contextualized patient personas. Nursing students (n=20) at the National University of Singapore completed a structured nine-item survey after engaging with avatar videos and attempting patient diagnosis, with a focus on psychosis and mania presentations. Items used 5-point Likert scales addressing learning enhancement, comparison with traditional methods, realism, retention, preference, subtle behavior detection, and clinical confidence; open-ended items captured specific experiences and challenges. All 20 students reported enhanced understanding of psychosis and mania (40% strongly, 60% moderately enhanced). Ninety-five percent rated the avatars more helpful than textbooks and lectures; 85% anticipated better knowledge retention; 85% preferred more avatar-based learning; 70% found the portrayal realistic; 70% reported improved detection of subtle symptoms; and 65% expressed confidence in applying knowledge to clinical scenarios. Qualitative feedback identified emotional expressivity and one-directional interactivity as primary limitations. These findings indicate that AI avatar-based psychiatric simulation is a feasible and well-received modality that recruits social cognitive and affective processes relevant to empathy, mentalizing, and clinical observation, consistent with neuroscience-informed principles of emotionally engaged learning. Enhancing emotional realism and enabling bidirectional interaction are priorities for the next generation of this platform.

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Poster

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Topic: I.06. Social Cognition

Support: NIMH Intramural Research Program (ZIAMH002781)
NIH Grant ZIAMH002781

Title: Self-Reported but Not Parent-Reported Irritability Predicts Amygdala-Frontoparietal Connectivity in Youth

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Abstract: Irritability is a proneness to anger that frequently presents with anxiety, ADHD, and depression. Translational models propose that irritability arises from aberrant emotional reactivity and responses to frustration, implicating amygdala and nucleus accumbens circuitry with prefrontal cortex (Brotman et al., 2017). However, findings linking irritability to these circuits have been inconsistent, often from small samples (Lee et al., 2023). Furthermore, few studies have directly compared the strength of neural associations across these symptom domains or tested whether effects are specific to the amygdala and nucleus accumbens relative to other subcortical regions. In this preliminary multisite analysis, we examined resting-state fMRI in N=1,181 youth (ages 7-22; 57% male) across three transdiagnostic cohorts. Self- and parent-reported irritability (Affective Reactivity Index; ARI) were each tested as predictors of amygdala and nucleus accumbens connectivity with cortical networks (Schaefer 400-parcel/17-network and 12 subcortical seeds), modeling comorbid symptoms simultaneously to test specificity, and covarying age, sex, head motion, and site. Self-reported ARI uniquely predicted right amygdala to frontoparietal control network connectivity (β=0.123, p=0.0004, FDR=0.016), while parent-reported ARI did not (p>0.1). No nucleus accumbens metric was significant. Formal comparisons confirmed that self-reported ARI was a significantly stronger predictor of amygdala-frontoparietal connectivity than anxiety, ADHD, and depressive symptoms (p<0.05). The effect was specific to the amygdala relative to 9 of 11 other subcortical regions (exceptions: bilateral hippocampus). These findings demonstrate that self-reported irritability is associated with intrinsic amygdala-frontoparietal connectivity in youth, supporting the threat/emotional reactivity pathway of translational models. The specificity to self-report suggests the child's subjective experience captures variance in amygdala circuitry not indexed by parent observation. The null finding for nucleus accumbens suggests the reward pathway may not contribute to irritability-related connectivity differences at rest. Additional data are being incorporated to increase sample size.

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Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

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Topic: I.06. Social Cognition

Support: NIMH Grant 1R21MH131928-01A1

Title: Exploring how social observation impacts relations between social anxiety and error monitoring for adolescents

Authors: *C. KNOWLTON[1], F. ZAKIROV[1], L. CRUZ[1], L. A. SAHAR[2], L. M. LAPLACE[1], J. W. PETTIT[1], A. M. MEDINA[2], G. A. BUZZELL[1];
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Abstract: Social anxiety disorder is an impairing condition that affects about 10% of the U.S. population. Social anxiety most commonly onsets during adolescence, and response rates for adolescent social anxiety are suboptimal. Prior work suggests socially anxious adolescents exhibit heightened error monitoring, which refers to the ability to self-detect and self-monitor errors. Error-related electroencephalogram (EEG) activity is commonly employed to index error monitoring by quantifying the event-related negativity (ERN). Emerging work has shown that social observation heightens the relationship between social anxiety and error monitoring. We sought to replicate this relationship in adolescents. Therefore, we examined parent-reported social anxiety symptoms in 10-18-year-olds (n = 76), as well as error monitoring, measured by the ERN, during a flanker task performed in social and nonsocial conditions. We tested whether social anxiety predicted the ERN, and whether this effect was further moderated by social observation. Contrary to prior work, results indicated that increased social anxiety predicted a weaker (i.e., more positive) ERN (p = .028). However, this association between social anxiety and the ERN was moderated by social observation (p = .048). Follow-up simple slopes analyses revealed that the ERN was only associated with a weaker ERN when participants performed the task alone (p = .004). Social observation dampened this unexpected effect but did not reverse it (p = .305). Theoretical implications of these results will be discussed.

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Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.20/KK47

Topic: H.04. Emotion

Support: NIMH Pathway to Independence Award (K99MH140055, PI: Henry)
NIMH Dr. Seymour S. Kety Memorial Fellowship (PI: Henry)
Intramural Research Program (IRP) of the NIMH (ZIAMH002778, PI: Brotman)

Title: Leveraging Personalized and Population-Level Machine Learning to Predict Temper Outbursts in Youth with Pediatric Irritability

Authors: *B. FAIZAL[1], A. GROSZKOWSKI[1], C. ZHENG[1], K. LEE[1], W. K. SILVERMAN[2], L. H. POWELL[3], G. R. HAYES[4], F. PEREIRA[1], D. S. PINE[1], M. A. BROTMAN[1], L. M. HENRY[1];
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Abstract: Introduction: Severe irritability in children is associated with temper outbursts that are impairing for families. Previous studies have identified population-level patterns to predict outbursts but less is known about the value of including personalized data. We use both group-level and individual information in machine learning algorithms and evaluate which approach has the best performance for predicting outburst risk.
Methods: A total of 1,839 ecological momentary assessment observations (3x/day) were collected across baseline, treatment, and follow-up (up to 21 weeks) from 5 families of children with clinically significant irritability (Mean age = 11.6; 100% male; 80% White). We developed gradient boosted decision tree models to predict outbursts using three approaches: population, personalized, and a blended model. For the population model, each subject was treated as a held-out test case, while the model was trained once using the full data from all other participants. The personalized model used an expanding window approach, training on each individual's prior observations to predict the next time point. The blended model combined the probabilistic predictions from the population and personalized models using an equal weight (k = 0.5). Model performance was evaluated by area under the curve (AUC), precision (proportion of predicted outbursts that were correct), recall (proportion of true outbursts correctly defined), and F1 score (harmonic mean of precision and recall).
Results: The personalized model achieved the strongest overall performance (AUC = 0.753; precision = 0.487, recall= 0.625, F1 score = 0.548). The population model showed lower performance across metrics (AUC = 0.592, precision = 0.341, recall = 0.233, F1 = 0.277). The blended model showed a balanced trade-off between precision and recall (precision = 0.541, recall = 0.560), with similar performance to the personalized model (AUC = 0.732, F1 = 0.551). Overall, models incorporating individual level data outperformed the population only approach.
Conclusion: Including personalized data improves performance of the prediction model. Findings highlight the importance of personalized modeling to capture the heterogeneity in affective dynamics across irritable youth. Future work will gather more data and recruit a more representative sample.

Disclosures: B. Faizal: None. **A. Groszkowski:** None. **C. Zheng:** None. **K. Lee:** None. **W.K. Silverman:** None. **L.H. Powell:** None. **G.R. Hayes:** None. **F. Pereira:** None. **D.S. Pine:** None. **M.A. Brotman:** None. **L.M. Henry:** None.

Poster

PSTR286: Neural Bases of Human Social and Affective Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR286.21/KK48

Topic: I.06. Social Cognition

Title: Virtual psychodiagnost based on a cognitive architecture and large language models

Authors: *A. V. SAMSONOVICH, A. DOLGIKH, A. LENKOV;
Natl. Res. Nuclear Univ. MEPhI, Moscow, Russian Federation

Abstract: The growing demand for accessible psychological assessment tools and the recent progress of large language models create an opportunity to move beyond rigid questionnaires toward adaptive, dialogue-based psychodiagnostic screening. This study presents an LLM-based virtual psychodiagnostic system designed to construct structured profiles of users' personality, cognitive, emotional, and behavioral characteristics through natural-language interaction. The proposed architecture combines a FastAPI backend, an LLM accessed through an external API, and a retrieval-augmented generation (RAG) module built on a two-level knowledge base consisting of a stable theoretical core and an expandable layer of external sources. Semantic retrieval is implemented using text-embedding-3-small embeddings and cosine similarity. The diagnostic model is organized hierarchically into quantitative Big Five scores, eight qualitative domains covering temperament, cognitive style, social traits, Schwartz values, representational systems, emotional state, moral schemas, and behavioral patterns, as well as a set of derived typological dichotomies. Dialogue management prioritizes underrepresented diagnostic domains and uses normalization of question skeletons to reduce semantic repetition while maintaining coverage over at least 12 exchanges. The prototype was evaluated in a two-stage pilot study: baseline standardized testing was conducted with 57 participants, and 15 participants completed diagnostic sessions in the system for comparison with standardized Big Five measures. Spearman correlations between system-generated Big Five scores and standardized test results ranged from 0.51 to 0.75 across the five traits and were statistically significant ($p < 0.05$). All 15 sessions produced substantive conclusions for all eight diagnostic domains and reported confidence values for each parameter, including warnings where information saturation was insufficient. These findings suggest that LLM-based psychodiagnostic screening can produce interpretable and empirically aligned personality profiles when constrained by psychometric models, retrieval-based theoretical grounding, and controlled dialogue management. The system is intended for non-clinical use in educational and research settings and should be considered an auxiliary screening tool rather than a substitute for professional psychological assessment.

Disclosures: A.V. Samsonovich: None. **A. Dolgikh:** None. **A. Lenkov:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.01/KK49

Topic: I.08. Learning and Memory

Support: JST SPRING, Grant Number JPMJSP2156
JSPS KAKENHI, Grant Number JP25KJ2001

The 40th Research Grant from the Meiji Yasuda Life Foundation of Health and Welfare

Title: Spatial cognitive demand mediates the effects of exercise on the dorsal hippocampus

Authors: *R. TSUCHIDA[1,2], T. YAMAGUCHI[1], A. NAGASAKI[1], H. ONISHI[1,2], R. NAOCHI[1], J. TAGAMI[1], M. SHIMODA[1], D. FUNABASHI[3], T. MATSUI[4], T. NISHIJIMA[1]; [1]Tokyo Metropolitan Univ., Tokyo, Japan; [2]Japan Society for the Promotion of Sci., Tokyo, Japan; [3]Hakuoh Univ., Tochigi, Japan; [4]Fac. of Hlth. and Sport Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: [Background] Exercise enhances hippocampal function and reduces the risk of cognitive decline, yet why exercise benefits the hippocampus, a brain region not required for motor execution, remains unclear. According to the principle of "use it or lose it," neural circuits adapt when actively recruited, suggesting that the hippocampus may be engaged during exercise through processes other than motor control. Among hippocampal subregions, the dorsal hippocampus plays a key role in spatial cognition. Exercise fundamentally consists of locomotion, and locomotion inherently entails continuous changes in spatial information. We therefore hypothesized that spatial cognitive demands accompanying exercise, rather than exercise itself, mediate exercise-induced dorsal hippocampal plasticity.[Methods & Results] Using acute and chronic mouse models, we manipulated spatial cognitive demands during exercise while matching exercise intensity and duration. (Experiment 1) Treadmill exercise alone activated spatial regions including the dorsal hippocampus and entorhinal cortex, whereas both treadmill and rotarod exercise activated non-spatial regions such as the ventral hippocampus and dorsal raphe serotonergic neurons. (Experiment 2) To test whether treadmill-induced dorsal hippocampal benefits depend on spatial cognitive demands, these demands were restricted by shortening the running lane. This attenuated acute exercise-induced dorsal hippocampal activation and reduced the effects of chronic exercise on neurogenesis and spatial working memory despite comparable exercise intensity, whereas activity in non-spatial regions was preserved. (Experiment 3) Conversely, to determine whether introducing spatial cognitive demands could confer dorsal hippocampal benefits to an exercise type that normally lacks them, we added spatial information to rotarod exercise. This intervention elicited dorsal hippocampal activation during acute exercise and promoted dorsal hippocampus-dependent memory performance, with a trend toward increased neurogenesis following chronic exercise. [Discussion] Across experiments, dorsal hippocampal activation and plasticity emerged only when spatial cognitive demands were engaged during exercise. These findings demonstrate that the dorsal hippocampal benefits of exercise are not determined solely by exercise itself but critically depend on the recruitment of spatial cognitive processes during exercise. Incorporating spatial cognitive demands into exercise may be essential for optimizing interventions aimed at preserving hippocampal function and preventing cognitive decline.

Disclosures: R. Tsuchida: None. **T. Yamaguchi:** None. **A. Nagasaki:** None. **H. Onishi:** None. **R. Naochi:** None. **J. Tagami:** None. **M. Shimoda:** None. **D. Funabashi:** None. **T. Matsui:** None. **T. Nishijima:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.02/KK50

Topic: I.08. Learning and Memory

Support: JST ERATO (JPMJER1801)
JSPS KAKENHI (22K21353)
AMED Brain/ MINDS 2.0 (24wm0625207s0101; 24wm0625401h0001; 24wm0625502s0501)
the Institute for Al and Beyond of the University of Tokyo
Kobayashi foundation
Smoking Research Foundation

Title: Nicotine withdrawal impairs object recognition memory and alters neural activity

Authors: *H. SUZUKI[1], K. IZUMO[1], K. KAKEHI[1], Y. IKEGAYA[1,2], N. MATSUMOTO[1,2]; [1]Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan; [2]The Inst. for AI and Beyond, The Univ. of Tokyo, Tokyo, Japan

Abstract: Nicotine, an alkaloid derived from tobacco leaves, acts as an agonist for nicotinic acetylcholine receptors in the brain. Activation of these receptors stimulates the dopaminergic system and reward pathway, leading to strong dependence. Because of this dependence, various withdrawal symptoms manifest during nicotine deprivation. Although these withdrawal symptoms pose a major barrier to smoking cessation, little research has linked them to neural activity. While molecular and behavioral aspects of nicotine withdrawal symptoms are well-documented, our findings identify the in vivo neural correlates that link these two levels. Therefore, this study focused on how nicotine withdrawal affects memory. To understand this process, we investigated neural activity in the hippocampus and prefrontal cortex.
First, we implanted nichrome-wired electrodes into the hippocampus and prefrontal cortex of mice. After a postoperative recovery period of several days, mice were administered nicotine in drinking water for two weeks. Specifically, the nicotine-treated group was given nicotine dissolved in a saccharin solution (an artificial sweetener) as drinking water, while the control group received only the saccharin solution. During this administration period, there were no differences in body weight or water intake between the two groups.At the end of the two-week chronic administration period, the first novel object recognition test was conducted. Subsequently, the drinking water was switched to regular tap water to induce withdrawal. After 24 hours of this withdrawal period, a second novel object recognition test was performed. Comparing the results of the first and second memory tests, we found that 24 hours of nicotine withdrawal resulted in a decline in memory performance.
Furthermore, we analyzed the local field potentials in the hippocampus and prefrontal cortex recorded during the memory tests. The local field potentials were decomposed into distinct frequency bands using a Fourier transform, and a Hilbert transform was applied to analyze the signal amplitudes. This analysis revealed significant changes in amplitude within specific

frequency bands before and after withdrawal. This suggests the possibility that these alterations in local field potentials are associated with the decline in memory.
While molecular and behavioral aspects of nicotine withdrawal symptoms are well-documented, our findings identify the in vivo neural correlates that link these two levels. Our study establishes a platform for further investigation into the neural and peripheral mechanisms underlying nicotine-induced cognitive changes.

Disclosures: H. Suzuki: None. **K. Izumo:** None. **K. Kakehi:** None. **Y. Ikegaya:** None. **N. Matsumoto:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.03/KK51

Topic: I.08. Learning and Memory

Support: SPARC Grant from UofSc
NIH-NCCIH (R00-AT010903)
NIH-NCCIH (R01-AT013234)

Title: Blue Light at Night Impairs Memory and Hippocampal Plasticity via Corticosterone Elevation in Adolescent Mice

Authors: *A. BHAN[1], P. BONILLA VILLAMIL[1], J. KARTIK[1], A. PORCU[2];
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Abstract: Adolescents are being increasingly exposed to artificial blue light at night from electronic devices, raising concerns about its effects on brain development and mental health. The hippocampus, and specifically the dentate gyrus (DG) regulates memory formation and itself operates as a subordinate circadian oscillator detecting changes in the light environment through alterations in corticosterone rhythm. Whether blue light at night during adolescence can impair hippocampal function via corticosterone remains unknown. To begin exploring this, we exposed adolescent mice to a light cycle disruption (LCD) paradigm consisting of 12hrs of light followed by 5hrs of darkness and 7hrs of blue light (12L:5D:7L) for 5 consecutive days per week, followed by a standard 12L:12D cycle for 2 days, over a 4-week period. Control animals were maintained under standard 12L:12D. Female and male mice were then tested for novel object recognition (NOR) and novel object location (NOL), and brain tissue was collected for clock gene expression, neuroplasticity, and dendritic spine integrity analyses. We found that male mice exposed to LCD spent less time exploring novel objects and locations, and more time with familiar ones, a pattern consistent with impaired recognition and spatial memory. LCD-exposed male mice showed disrupted daily expression rhythms of Bdnf, Clock, CRY2 and corticosterone levels compared to male control and LCD-exposed females. In addition, we found that LCD-

exposed males also exhibited reduced p-CREB and doublecortin expression along with reduced dendrite spines numbers in the DG. Interestingly, returning LCD-exposed males to standard 12L:12D conditions for 4 weeks was sufficient to reverse both the behavioral and molecular phenotypes. Together, these results suggest that chronic exposure to blue light at night during adolescence impairs memory in male mice by destabilizing circadian clock gene rhythms, elevating corticosterone, suppressing neuroplasticity and spine integrity in the DG.

Disclosures: A. Bhan: None. **P. Bonilla Villamil:** None. **J. Kartik:** None. **A. Porcu:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.04/KK52

Topic: I.08. Learning and Memory

Title: Effects of acute and chronic ball playing on hippocampus in adolescent mice

Authors: *R. MURATA[1], R. NAOCHI[1], H. ONISHI[1,2], R. TSUCHIDA[1,2], J. TAGAMI[1], M. SHIMODA[1], T. NISHIJIMA[1];
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Abstract: [Background] Excessive screen time has emerged as a major concern because of its association with impaired prefrontal and hippocampal function. Physical activity promotes healthy brain development and may serve as an alternative to screen-based activities. Although exercise enhances hippocampal function, it remains unclear how play, a major component of children's physical activity, influences the hippocampus. Therefore, this study investigated whether acute and chronic ball playing modulate hippocampal neural activity and hippocampal function in adolescent mice. [Methods and Results] Experiment 1: Do mice show a preference for balls? 5-week-old male C57BL/6J mice were allowed to freely explore a three-chamber apparatus for 20 min. The apparatus consisted of a central area without balls (Central area), an area with floor-fixed balls (Fixed area), and an area with freely movable balls (Free area). Mice spent significantly more time in the Fixed area than in the Central area and more time in the Free area than in the Fixed area. Experiment 2: Does acute ball playing enhance hippocampal neural activity?Mice were exposed to an open field (OF) for 30 min. They were assigned to one of four groups: Naïve (no exposure), Open (OF without balls), Fixed (OF with floor-fixed balls), and Free (OF with freely movable balls). Five balls from three types were used. Hippocampal neural activity was assessed after exposure. Hippocampal neural activity was elevated in the Fixed and Free groups relative to the Open and Naïve groups and was the highest in the Free group. Experiment 3: Does chronic ball playing improve hippocampal function? The Open, Fixed, and Free groups were exposed to the OF for 4 weeks (30 min/day, 5 days/week). To maintain novelty, the number and combination of balls were varied across sessions (1-3 balls). During the

final week, hippocampal-dependent behavior was assessed, and neural activity and neurogenesis were evaluated on the final day. The Free group exhibited elevated neural activity during the final exposure session. However, no significant differences were observed among groups in hippocampal-dependent behavior or neurogenesis. [Conclusion] Mice preferred ball-containing environments, particularly those with movable balls. Acute ball playing enhanced hippocampal neural activity. In contrast, chronic ball playing did not improve hippocampal-dependent behavior or neurogenesis under present condition. However, sustained neural activity suggests that ball playing remains capable of activating the hippocampus even after repeated exposure, and that alternative conditions may reveal beneficial effects of chronic ball playing.

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Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.05/KK53

Topic: I.08. Learning and Memory

Support: DFG SFB 1280 “Extinction Learning” Project Nr. 316803389

Title: Taken out of context - Disentangling stimuli and context in extinction learning

Authors: *R. PUSCH[1], O. GUNTURKUN[2];
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Abstract: The phrase “Taken out of context” underscores that adaptively interpreting things, be they quotes, events, actions, or stimuli, does not happen in isolation. Rather, all assessments are embedded in a bigger picture - their respective context. Even if one has a subjective understanding of context, it is difficult to provide a comprehensive definition. Is context established by stimuli with inherent properties or can other sensible stimuli subconsciously be incorporated into a context plan - including time as an internal state / interoceptive information not experienced by the primary senses? Thus, here we ask the very simple question: What is context? And what are the circumstances allowing a stimulus to become “contextual”? To address these questions, we investigated extinction learning, the gradual decrease and eventual elimination of a learned behavior and its subsequent renewal, the context-dependent relapse of initially learned behavior in pigeons (*Columba livia*). Using an ABA extinction learning paradigm, we assessed how competing stimuli and time induced contextual renewal during extinction learning. We followed a two-stranded experimental approach: In the first strand we conducted experiments in a large arena to pit different contextual stimuli, against each other. These included the background of the screens where the stimuli were presented (local stimuli),

larger landmarks (global stimuli) and large environmental cues (environmental stimuli). In the second strand, we tested the influence of stimulus parameters like contingency and the influence of time on renewal in Skinner boxes. Counterintuitively we found that local stimuli elicited the highest amount of renewal responses and violations with respect to reward contingency delayed extinction learning and hindered subsequent renewal. Time could also act as a context in our paradigm and resulted in robust renewal responses. Combining our behavioral results with electrophysiological recordings in the extinction network, we provide a mechanistical understanding of how context is neuronally represented and gains control over behavior. Our research suggests that context does not represent a qualitatively distinct category of stimuli but rather is learned through the same reward contingency mechanisms as discrete cues. Ultimately, we propose that context can be understood as a learned stimulus property.

Disclosures: R. Pusch: None. **O. Gunturkun:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.06/KK54

Topic: I.08. Learning and Memory

Support: R01 HL166608

Title: Cardiovascular Kidney Metabolic Syndrome as a Risk Factor for Neurocognitive Decline

Authors: *F. CHOWDHURY[1], H. PAUL[1], S. LOTFOLLAHZADEH[1], A. O'CONNELL[2], W. BRENNAN[2], N. CROSSLAND[2], J. K. BLUSZTAJN[2], T. J. MELLOTT[2], V. CHITALIA[1]; [1]Nephrology, [2]Pathology & Lab. Med., Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: Cardiovascular-kidney-metabolic (CKM) syndrome is a systemic disorder characterized by the pathophysiological interplay among metabolic risk factors (obesity, type 2 diabetes), chronic kidney disease (CKD), and cardiovascular disease. CKM syndrome risk factors affect the majority of U.S. adults. A key component of CKM syndrome is CKD, which itself affects approximately 1 in 7 U.S. adults, and whose presence accelerates progression through the CKM continuum. Epidemiological evidence indicates that CKM syndrome confers a risk for cognitive decline and dementia. Despite this recognition, the mechanisms linking CKM syndrome to neurological dysfunction remain poorly understood. To address this knowledge gap, we developed a novel mouse model of CKM syndrome combining unilateral nephrectomy with exposure to Western and cafeteria diets to recapitulate the metabolic and renal abnormalities commonly observed in human disease.
This model induced a phenotype characterized by renal dysfunction, insulin resistance, hypertriglyceridemia, myocardial fibrosis, and hepatic steatosis—hallmark features of CKM

syndrome. Mice were subjected to behavioral assessment after 6 and 12 weeks on the diet using open field and novel object recognition paradigms. At both time points, CKM syndrome mice demonstrated significant impairment in cognitive performance, including reductions in normalized novel object recognition, absolute object discrimination ($p < 0.01$), and relative object discrimination ($p < 0.05$) compared with controls. In contrast, measures of locomotion and anxiety-related behavior—including mobility, activity, total distance traveled, velocity, and time spent in the center of the open field apparatus—remained unchanged, suggesting a selective impairment in cognition rather than generalized behavioral dysfunction.
Collectively, these findings establish an experimental model of CKM syndrome-associated neurocognitive decline and provide evidence that combined renal and metabolic dysfunction impairs cognition. The model provides an opportunity to investigate molecular mechanisms linking CKD, metabolic disease, and neuronal dysfunction, and may facilitate identification of therapeutic strategies to mitigate cognitive decline in patients with CKM syndrome.

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Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

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Program #/Poster #: PSTR287.07/Web Only

Topic: I.08. Learning and Memory

Support: EPM(1) 2024 Grant, CVU: 771574

Title: Effect of a mind-body technique on the neuronal pattern of the retrieval of information

Authors: *U. CABALLERO SANCHEZ[1], A. LÁZARO-FIGUEROA[4], E. GARCÍA TREJO[2], E. LÓPEZ-GONZÁLEZ[5], A. RUIZ-CONTERARAS[6], S. ROMERO HIDALGO[3]; [1]INMEGEN, Mexico City, Mexico; [2]INMEGEN, Tequisquiapan, Mexico; [3]INMEGEN, Mexico city, Mexico; [4]Univ. Nacional Autonoma de Mexico, Mexico, City, Mexico; [5]LNGC, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico; [6]Univ. Nacional Autonoma de Mexico, Ciudad de México, Mexico

Abstract: QiGong is a mind-body technique (i.e., a set of movements and breathing that emphasize the interaction between mental processes -consciousness- and bodily functions) that consists of a fixed sequence of movements and conscious breathing. Several studies have associated QiGong practice with improvements in different cognitive domains. In addition, QiGong practice has been linked to changes in brain oscillatory activity, including theta, which is known to be associated with episodic memory retrieval. As far as we know, there are no studies that examine the relationship between QiGong practice and episodic memory. Therefore, this

study explored the possible association between neuronal patterns related to episodic memory retrieval and ZhiNeng QiGong practice (ZNQG), a specific form of QiGong. Event-Related Potentials (ERPs) during a know-remember recognition task were obtained from beginners (29 adults with low or no ZNQG experience) and experienced practitioners (23 adults with more than one year of practicing ZNQG). The task consisted of two phases: encoding and retrieval. During encoding, participants classified images as natural or artificial. During retrieval, participants classified each stimulus as new (image not presented during the encoding phase), known (recognizing the image only through familiarity with no associated context), and remembered (recognizing the information with some specific context). To increase the number of epochs available for the analysis, known and remembered responses were combined into a single category of correct retrieval, whereas correct rejections were all new items correctly identified. Results showed that beginners have higher amplitude than experienced in frontal region (i.e., Fz; corrected $p = 0.034$) in the 326 to 588 ms window, regardless of response type (i.e., correct retrieval and rejection). In addition, a negative correlation was found between the frequency of ZNQG practice and the Fz amplitude in the 326 to 588 ms window for the correct rejection and correct retrieval (correct rejection: $\rho = -0.44$, corrected $p = 0.02$; correct retrieval: $\rho = -0.43$, corrected $p = 0.02$). Moreover, amplitudes at F3 and F8 during a later time window (618 to 644 ms) were negatively correlated with practice frequency for correct retrieval only (F3: $\rho = -0.47$, corrected $p = 0.01$; F8: $\rho = -0.42$, corrected $p = 0.02$). No behaviorally significant differences were observed between groups. These results suggest that the practice of ZNQG improves the neuronal efficiency to retrieve information: fewer synchronized neurons are necessary to obtain the same behavioral efficiency.

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Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.08/KK55

Topic: I.08. Learning and Memory

Support: Canadian Institutes of Health Research #175086

Title: Sex differences in the effect of deep brain stimulation on a model of traumatic brain injury

Authors: T. RABELO[1], I. ROBSON[1], *C. HAMANI[2];
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Abstract: Traumatic brain injury (TBI) is associated with cognitive impairments, with episodic memory deficits among the most common and disabling sequelae. Clinical evidence suggests

that females experience worse long-term cognitive outcomes following TBI; however, biological sex remains underexplored in preclinical neuromodulation studies. Deep brain stimulation (DBS) is a promising approach for cognitive rehabilitation, but its sex-dependent efficacy after TBI is not well understood. We investigated the effects of chronic anterior nucleus of the thalamus (ANT)-DBS on spatial learning and recognition memory following moderate-to-severe lateral fluid percussion (LFP) injury in female (n=72, 234-318 g) and male (n=65, 225-320 g) rats. Animals were implanted with bilateral ANT-DBS electrodes three days after LFP. Beginning seven days after TBI, animals received either active or sham stimulation (6 h/day for 7 days; 3 h/day for 8 days). Thirteen days after TBI, they were tested using novel object/novel location recognition and the Barnes maze. Vaginal lavage samples were collected during behavioral testing. We found that TBI produced sex- and domain-specific cognitive impairments. While females showed greater deficits in novelty-based recognition memory, males had greater impairments in spatial acquisition. ANT-DBS improved outcomes in a pattern that reflected these vulnerabilities, most notably restoring recognition memory in females. Electrode implantation without stimulation also improved several outcomes, suggesting insertion-related effects. DBS increased spatial search strategies in the Barnes maze, with similar effects across sexes. These findings demonstrate the potential of ANT-DBS to improve cognitive outcomes after TBI in a sex- and task-dependent manner and highlight the importance of considering biological sex in the application of neuromodulatory therapies.

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Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.09/KK56

Topic: I.08. Learning and Memory

Support: Biomedical Research Center, UV
SECIHTI to CAM-C (No. 838990
SECIHTI Postdoctoral Academic Stay for Indigenous Women to HM-P (CVU: 513312)

Title: Effects of a hypercaloric diet on oxidative/nitrosative stress markers, peripheral inflammation, and spatial learning in male and female CD-1 mice

Authors: C. MENDOZA[1], H. MARTÍNEZ-PACHECO[2], C. J. JUÁREZ-PORTILLA[3], V. HERNÁNDEZ ESLAVA[4], R. VIVEROS CONTRERAS[5], T. MOLINA-JIMENEZ[6], G. R. ROLDAN[7], ***R. C. ZEPEDA**[5];
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Abstract: Excessive consumption of ultra-processed foods, which are high in fat and refined sugars, combined with sugary beverages, has accelerated the rise in obesity rates. This consumption has been associated with alterations in the hippocampus, the region involved in learning and spatial memory; however, the exact mechanisms remain uncertain. Since these alterations do not present physical manifestations or impairments that impact quality of life, they may remain unnoticed for several years. Therefore, this study evaluated the impact of a high-fat, high-sucrose diet (HF-HSD) on locomotor activity, learning, and spatial memory, as well as markers of oxidative/nitrosative stress and peripheral and central inflammation in male and female CD-1 mice. After 17 weeks of HF-HSD, animals showed reduced locomotor and exploratory performance in the open field. In cognitive tests, impairment was most evident in tasks with high spatial demands, particularly in the T-maze, where the diet was associated with poorer learning performance and deficits in short- and long-term memory tests. This pattern was consistent with results from novel place recognition and contrasted with a less marked impairment in novel object recognition, suggesting a preferential vulnerability of spatial circuits. These cognitive impairments are strongly related to the oxidant/nitrooxidant profile we found in the hippocampus and to elevated proinflammatory cytokines in serum. Taken together, the findings support the notion that HF-HSD in CD-1 mice reproduces relevant metabolic and neurobehavioral components of diet-induced obesity—previously reported by our research group—integrating adiposity, metabolic impairment, redox stress/inflammation, and spatial memory impairments with sex-dependent differences.

Disclosures: C. Mendoza: None. **H. Martínez-Pacheco:** None. **C.J. Juárez-Portilla:** None. **V. Hernández Eslava:** None. **R. Viveros Contreras:** None. **T. Molina-jimenez:** None. **G.R. Roldan:** None. **R.C. Zepeda:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.10/KK57

Topic: I.08. Learning and Memory

Support: ERC Grant N. 101125658

Title: Hippocampal-Parietal Dissociation in Mapping and Moving Through Conceptual Space

Authors: *G. GIARI, R. BOTTINI;
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Abstract: How do we search for concepts in memory? Two phenomena have been recently reported: hippocampal theta power scaling with semantic distance, suggesting repurposing of spatial navigation mechanisms; spontaneous eye movements reflecting conceptual distance, suggesting a potential role of attention in moving through conceptual space.Here we set out to investigate their relationship using magnetoencephalograhy and eye tracking. Participants performed multiple blocks of a verbal fluency task in the conceptual space of numbers while static visual noise was presented to them.First, we replicated previous findings showing that eye movements were modulated by the signed transition distance between numbers, reflecting the structure of the conceptual space: transitioning to a lower number is reflected in a gaze shift towards the left, while shifts to the right occurred when transitioning to a higher number.At the neural level, we showed that hippocampal theta power scaled with the value of the number participants were about to say (e.g., 2, 7, 9, etc.), independently of preceeding and following numbers. Precuneus theta power, instead, scaled with the absolute distance of the transition between subsequent numbers (e.g., 2 followed by 7 is a transition distance of 5 and 7 followed by 2 is also a transition distance of 5). These effects suggest a functional dissociation between brain areas: the hippocampus represents the map-like, allocentric structure of the conceptual space; precuneus instead represents distances, or movements, in the conceptual space from an egocentric perspective, possibly reflecting its influence on attention and eye movements.To evaluate the relationship between eye- and neural-effects we then estimated their latency. As predicted, we found that these effects emerged following a linear trend: first, transition magnitude was reflected in precuneus theta power; second, the eyes moved following the signed transition; third, hippocampal theta power was modulated by the value of the number to be said. A movement signal was thus generated in parietal cortex and, after executing the movement through the eyes, position in the conceptual space was updated in the hippocampal map.We here provided evidence describing a mechanism through which coordinated theta oscillations and eye movements allow exploration of conceptual spaces. Even when there is nothing to see, eye movements may act as an embodied signal of movement in conceptual spaces whose timely execution is coordinated with theta power in the hippocampus, a key node of the spatial navigation system, and precuneus, a key node of the attentional network.

Disclosures: G. Giari: None. **R. Bottini:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.11/KK58

Topic: I.08. Learning and Memory

Title: Memory enhancement in trained mice by 3BDO-mediated mTORC1 activation is accompanied by nucleolar subcompartment remodeling in hippocampal neurons

Authors: J. ZENG[1], H. LU[2], W. WANG[2], M. WONG[2], *G. P. BAENA-CALDAS[1], O. HE[1], C. ZHU[3], I. OJIMA[4], J. M. LIBIEN[1,5], A. I. HERNANDEZ[1,5];
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Abstract: The nucleolus contains three liquid-phase-separated subcompartments: the fibrillar center (FC), the dense fibrillar component (DFC), and the granular component (GC). Our previous research demonstrated that mTORC1 activation by 3BDO enhances weak active place avoidance (APA) training into a strong training protocol, thereby improving 24-hour memory. This memory enhancement by 3BDO relies on the upregulation of ribosomal RNA biogenesis. We hypothesize that nucleolar activation by 3BDO may alter nucleolar structure during the learning process. In this experiment, we evaluated whether triple immunofluorescent staining could detect changes in nucleolar subcompartments in hippocampal CA1 neurons following APA training, with or without 3BDO treatment. Wild-type mice were assigned to three groups: (a) untrained controls, (b) trained animals treated with 3BDO, and (c) trained animals treated with a vehicle solution. Following sacrifice, brain sections were stained with UBF, Fibrillarin, and Nucleophosmin/NPM1 antibodies to detect the FC, DFC, and GC nucleolar subcompartments, respectively. Animals trained without 3BDO exhibited increased nucleolar subcompartment signal intensities, particularly within the GC subcompartment, compared with untrained controls, indicating enhanced nucleolar activity during spatial learning. Furthermore, 3BDO treatment further enhanced the nucleolar signal intensities in trained animals, producing a synergistic effect on nucleolar activity. Additionally, 3BDO caused a conspicuous dissociation of the FC-DFC complex from the GC, suggesting that nucleolar organization was structurally altered. Ultimately, these findings demonstrate that triple-immunofluorescence of nucleolar subcompartments is an effective method for analyzing nucleolar structure and that 3BDO noticeably modulates nucleolar processes and morphology. Our results suggest that this technique is highly applicable for understanding the changes induced by mTORC1 in memory enhancement and may also serve as a potential biomarker in diseases characterized by altered nucleoli, such as Alzheimer's disease.

Disclosures: J. Zeng: None. **H. Lu:** None. **W. Wang:** None. **M. Wong:** None. **G.P. Baena-Caldas:** None. **O. He:** None. **C. Zhu:** None. **I. Ojima:** None. **J.M. Libien:** None. **A.I. Hernandez:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.12/KK59

Topic: I.08. Learning and Memory

Title: Closed-loop stimulation reveals learning-related plasticity in paired human brain organoids

Authors: C. ROUNTREE[1], E. SCHMIDT[1], N. COUNGERIS[2], V. ALSTAT[2], A. LACROIX[2], M. J. MOORE[3], *T. VU[4], C. M. BUTT[2];
[1]R&D, 28bio, Inc., Metairie, LA; [2]R&D, 28bio, Inc., Maple Grove, MN; [3]Biomed. Engineering, Tulane Brain Inst., Tulane Univ., New Orleans, LA; [4]HumanX Lab, Dartmouth Col., Hanover, NH

Abstract: Learning and memory dysfunction are major targets in central nervous system (CNS) drug discovery, but human-relevant functional biomarkers of synaptic plasticity remain limited. We developed a custom 24-well embedded-electrode array linking two human cortical organoids, derived from induced pluripotent stem cells, by guided axonal outgrowth. Organoid pairs (N=408) formed continuous inter-organoid neurite bundles over 2-5 weeks across 2-9 mm separations, and spontaneous bursting and evoked spiking increased with maturation. We then tested whether structured stimulation induced network-level long-term potentiation (LTP). In open-loop experiments, trained and untrained organoid pairs were evaluated each day with the same charge-balanced biphasic test-stimulation to quantify evoked responses relative to baseline. Trained pairs then received an additional stimulation designed to induce LTP, whereas untrained controls received only the daily evaluation sequence. Training increased evoked spike counts above day 0 baseline by day 2 in control medium (N=19) and reached 3-4x baseline by day 4 when brain-derived neurotrophic factor (BDNF, 50 ng/mL; N=12) was added. Blockade of N-methyl-D-aspartate receptor (NMDA-R) activity with AP5 (200 μM; N=12) abolished all potentiation. We next implemented a closed-loop maze game task in which directional stimuli were delivered to embody organoids in the game. Movement was controlled through organoid activity and trained with reward/penalty feedback. Pairs trained with a high-frequency penalty burst improved game performance and survival time over 1 week relative to untrained controls (N=8). Removing BDNF eliminated training-related gains (N=9). Bulk RNA sequencing (3 pooled samples/condition) showed that learning, memory, and synaptic-plasticity gene-set scores were elevated in trained control/BDNF conditions, and they were reduced by NMDA-R blockade or BDNF removal, paralleling electrophysiological and game outcomes. These findings establish paired human organoid networks as a platform for modeling learning-related plasticity and screening interventions that target CNS dysfunction.

Disclosures: C. Rountree: A. Employment/Salary (full or part-time):; 28bio, Inc. **E. Schmidt:** A. Employment/Salary (full or part-time):; 28bio, Inc. **N. Coungeris:** A. Employment/Salary (full or part-time):; 28bio, Inc. **V. Alstat:** A. Employment/Salary (full or part-time):; 28bio, Inc. **A. LaCroix:** A. Employment/Salary (full or part-time):; 28bio, Inc. **M.J. Moore:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 28bio, Inc.. **T. Vu:** None. **C.M. Butt:** A. Employment/Salary (full or part-time):; 28bio, Inc..

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.13/KK60

Topic: I.08. Learning and Memory

Title: Genetic variation in the NR4A2 gene linked to Neurodevelopmental Disorders and Parkinsonism causes sex-specific memory and motor impairments

Authors: *L. LANGMACK[1], T. ABEL[2];
[2]Dept. of Neurosci. and Pharmacol., [1]Univ. of Iowa, Iowa City, IA

Abstract: Neuronal activity directs gene expression programs and paves new circuits in the brain following a learning experience. Activity-induced gene expression upregulates immediate-early genes, like Fos, Arc, Egr1, Nr4a1, and Nr4a2, encoding key transcriptional regulators. Nr4a2 encodes a nuclear receptor DNA-binding transcription factor that is induced by CREB following activation of neuronal cell-types in the brain. The NR4A2 gene is linked to human cognition and now NR4A2 genetic variation is linked to intellectual and developmental disorders (IDDs). Using phenotypic data collected from people with Nr4a2-related neurodevelopmental disorder and the Simon's Foundation SPARK research study, we discovered that people with NR4A2 variants have higher symptom severity of Autism Spectrum Disorder (ASD), including restricted and repetitive behaviors and significant speech delay, and greater motor impairments than observed in the overall SPARK ASD cohort. We investigated the role of the most common reported variants, NR4A2 deletion/truncation and missense variants, in two mouse models. We find that male and female mice with Nr4a2 deletion and male missense variant R319Q mice, but not the females with R319Q, show impairments in spatial and contextual fear memory. Interestingly, male and female deletion mice are hyperactive, but male and female R319Q mice have motor coordination deficits. This reflects the range of symptoms reported in people with Nr4a2-related neurodevelopmental disorder and suggests that a missense variant might be more damaging to brain regions involved in motor function than a deletion of Nr4a2.

Disclosures: L. Langmack: None. **T. Abel:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.14/KK61

Topic: I.08. Learning and Memory

Support: HHMI Investigators Program

Title: Circuits for memory in food-caching birds

Authors: *R. HUSZAR[1], A. WAKHLOO[2], S. N. CHETTIH[3], D. ARONOV[4];
[1]HHMI / Columbia Univ., New York, NY; [3]Zuckerman Inst., [2]Columbia Univ., New York, NY;
[4]Columbia Univ. & HHMI, New York, NY

Abstract: Here, we study the circuits that underlie episodic memory in black-capped chickadees. These birds rely on their hippocampus to cache and retrieve thousands of food items scattered throughout their large territories. Similar to rodents, excitatory neurons in the chickadee hippocampus are place cells that fire in discrete locations of a physical space. During caching, however, place coding is suppressed, and the hippocampus produces a sparse pattern of activity, the "barcode", which uniquely identifies each cache. To explain barcode formation, we developed a circuit model involving two classes of interneurons: one providing strong inhibition during caching, and another that is recurrently coupled to excitatory cells. These modeling choices were motivated by physiologically distinct interneuron subtypes that are strongly activated (type 1) and suppressed (type 2) by caching, respectively. This model suggests that type 1 inhibition stabilizes high-dimensional activity to produce barcodes unique to each cache. To assess the connectivity of the relevant cell types in vivo, we recorded from hundreds of hippocampal neurons using Neuropixels probes while chickadees cached in a custom arena. These recordings were extended with light-off periods during which birds rested before and after behavior. We inferred putative monosynaptic connections from fine-timescale spiking synchrony using an approach that has been extensively validated against ground-truth data in rodents. We detected both excitatory and inhibitory connections, which allowed us to analyze the inputs and outputs of type 1 and type 2 interneurons. Type 1 cells received half as many excitatory inputs as type 2 interneurons. However, they provided stronger inhibitory output to excitatory neurons. These findings are broadly consistent with our model. Building on this baseline connectivity scheme, we will test whether caching rewires excitatory or inhibitory connectivity of neurons that participated in distinct caching episodes.

Disclosures: R. Huszar: None. **A. Wakhloo:** None. **S.N. Chettih:** None. **D. Aronov:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.15/KK62

Topic: I.08. Learning and Memory

Title: An exploratory behavioral and electroencephalographic (EEG) study of different modes of AI-assisted learning in high-school students (2026)

Authors: K. KHURANA[1], A. LIEW[1], *L. L. BELLINGER[2,3];
[1]Allen High Sch., Allen, TX, ; [2]Bioimedical Sci., [3]Biomed. Sci., Texas A&M Univ. Col. of Dent., Dallas, TX

Abstract: As artificial intelligence (AI) rapidly integrates into education, concerns have emerged regarding its potential influence on cognitive engagement and problem-solving behavior. However, existing research largely treats AI exposure as a binary condition (no-AI vs. AI), with limited differentiation between interaction modalities and post-exposure effects. This study addresses this by investigating whether distinct modes of AI interaction (Tutor, Collaborator, Solver) influence frontal EEG spectral activity. EEG data and quantified behavioral metrics were recorded from 48 participants (24 males, 24 females; ages 14-18) across 2 counterbalanced quizzes. The research plan was assessed and approved by the Allen High School IRB prior to data collection. Data collection was conducted in a controlled testing environment with standardized lighting, minimized noise, stable room temperature (75°F), and consistent EEG configuration (SereniBrain EEG Neurofeedback Headband Model TH21A) across all sessions. Statistical analyses included Friedman tests, repeated-measures ANOVA, paired t-tests, and Cohen's kappa calculations. Behavioral changes were mathematically analyzed in an observation matrix of 3 characteristics - initiation, processing, and stress - measured on an ordinal scale. Each mode showed significant differences in all three behavioral measures (Friedman test, $p < 0.0001$). Although the EEG differences did not reach statistical significance, descriptive oscillatory patterns were observed across the three AI interaction modes that should be expanded upon in future iterations. Exploring individual AI interaction modes revealed a possibility for heightened frontal oscillatory dynamics with Tutor and Collaborator modes and suppressed spectral dynamics in Solver mode. Descriptive comparisons suggested a possible short-term carryover phenomenon following AI interaction, leading to lower engagement-related oscillatory activity in subsequent independent tasks. This study provides preliminary behavioral evidence and exploratory electrophysiological observations, suggesting possible differences in neural activity and behavior based on AI interaction type, while establishing a replicable framework for future human-AI interaction studies. District IRB approval, risk assessment approval, and participant + parent consent forms available upon request.

Disclosures: K. Khurana: None. **A. Liew:** None. **L.L. Bellinger:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.16/KK63

Topic: I.08. Learning and Memory

Support: Whitehall 2023-08-050

Title: Engram silencing reveals context-specific memory deficits despite widespread hippocampal network perturbation

Authors: *W. SUN[1], K. LOPEZ[2], A. K. BOYCE[1], C. F. VALENZUELA[3], S. A. MCKENZIE[4]; [1]Univ. of New Mexico, Albuquerque, NM; [2]Univ. of New Mexico Dept. of Neurosciences,

Albuquerque, NM; [3]Dept Neurosci, Univ. New Mexico HSC, Albuquerque, NM; [4]Neurosciences, UNM HSC, Albuquerque, NM

Abstract: Recent memory retrieval depends on the neurons that expressed immediate early genes at the time of learning, known as “engram neurons”. However, the mechanisms by which engram neurons drive memory retrieval remain unclear. Previous study showed engram connectivity is important for retrieving memories and that a substantial fraction of neurons active during retrieval were not active during encoding. We therefore hypothesized that engram neurons work collectively with their surrounding neurons during retrieval to support memory expression. To address this hypothesis, we combined engram tagging, *in vivo* electrophysiological recording, optogenetics, and contextual fear conditioning to examine how hippocampal engram ensembles regulate contextual memory retrieval. We used two activity dependent labeling strategies, the Robust Activity Marking (RAM) system and the TRAP2 system, to target the cFos expressing neurons during contextual memory formation. By co-implanting silicon probes and optic fibers in dCA1, we monitored ensemble activity during memory retrieval while optogenetically perturbing labeled neurons. Although the overall sizes of the labeled populations appeared comparable based on fluorescent marker expression, the two labeling strategies produced distinct physiological effects. Optogenetic silencing of RAM labeled neurons induced widespread suppression of CA1 population activity, whereas silencing of TRAP2 labeled neurons produced sparse modulation consistent with the size of the fluorescently labeled population. We next asked whether these distinct network effects contributed similarly to behavioral memory expression. Using the same labeling approaches during contextual fear conditioning, we inhibited labeled ensembles during retrieval. Silencing RAM labeled ensembles impaired contextual fear memory, whereas silencing TRAP2 labeled ensembles did not produce a comparable impairment. Importantly, despite the widespread suppression observed after RAM labeled ensemble silencing, optogenetic disruption of freezing remained specific to the tagged context and did not generalize to a non-tagged, but shock-associated context. Together, these results suggest that hippocampal engram ensembles may support memory retrieval by recruiting a broader, context specific network beyond the initially activated population. Moreover, memory retrieval may depend on an engram regulated network that is dissociable from global neural activity. This work provides insight into how hippocampal engram neurons orchestrate circuit level activity to support contextual memory retrieval.

Disclosures: W. Sun: None. **K. Lopez:** None. **A.K. Boyce:** None. **C.F. Valenzuela:** None. **S.A. McKenzie:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.17/KK64

Topic: I.08. Learning and Memory

Support: 5R00AG078501

Title: SMAD2 Signaling Regulates Hippocampal Memory in Adult, Aging, and APP/PS1 Mice

Authors: *P. BHUIYAN[1], S. HUCKABEE[2], J. M. JUDD[2], M. FRITZ[1], E. B. WRIGHT[2], A. A. KEISER[1];
[1]Neurodegenerative Dis. Res. Ctr., Arizona State Univ., TEMPE, AZ; [2]Neurodegenerative Dis. Res. Ctr., Arizona State Univ., Tempe, AZ

Abstract: Disruption of gene expression and synaptic plasticity, which are essential for memory formation, are associated with age-associated cognitive decline and Alzheimer's disease (AD). Phosphorylated SMAD2 (p-SMAD2), a key regulator of TGF-β signaling, is aberrantly retained in the cytoplasm rather than translocating to the nucleus in AD, suggesting disrupted SMAD2-dependent transcriptional regulation of memory-related genes. However, whether SMAD2 phosphorylation is both essential and sufficient for hippocampus-dependent memory in healthy contexts or whether enhancing SMAD2 phosphorylation can reverse cognitive function in aging and AD remain unexplored. To address this question, we generated AAV1 vectors expressing phospho-mimetic *Smad2*$^{S464D, S465D, S467D}$, phospho-null *Smad2*$^{S464A, S465A, S467A}$, or control empty vector (EV) constructs. We confirmed the expression of these constructs by western blot analysis. To test whether disrupting endogenous SMAD2 phosphorylation is required for hippocampal memory formation, phospho-null *Smad2*$^{S464A, S465A, S467A}$ or EV were expressed through stereotaxic viral delivery into CA1 region of hippocampus in 3-month-old C57BL6 mice. To determine whether enhancing SMAD2 phosphorylation improves memory function, phospho-mimetic *Smad2*$^{S464D, S465D, S467D}$ was overexpressed in the CA1 region of 20-month-old C57BL6, as well as 13-month-old 129S6 SvEv and APP/PS1 male and female mice. Hippocampus-dependent memory was assessed utilizing the Object Location Memory (OLM) task. Phospho-null *Smad2* significantly impaired OLM performance relative to controls, confirming that intact p-SMAD2 signaling is required for normal memory formation. In 20-month-old senescent C57BL/6 mice, phospho-mimic *Smad2* significantly improved performance in the OLM compared to age-matched controls. Similarly, phospho-*Smad2* over-expression significantly enhanced OLM performance in both 129S6/SvEv wild-type and APP/PS1 transgenic mice compared with EV mice, indicating that SMAD2 phosphorylation is sufficient to counteract amyloid-driven cognitive decline. In separate cohorts, subcellular fractionation was conducted to evaluate the localization of p-SMAD2 in cytoplasmic and nuclear fractions during the 1-hour memory consolidation window. Mechanistically, phospho-mimetic *Smad2* increased nuclear localization of p-SMAD2 during memory consolidation, consistent with canonical nuclear SMAD2 transcriptional signaling. Together, these findings identify SMAD2 signaling as a functional regulator for hippocampus-dependent memory with potential therapeutic strategy for age-related memory decline and AD.

Disclosures: P. Bhuiyan: None. **S. Huckabee:** None. **J.M. Judd:** None. **M. Fritz:** None. **E.B. Wright:** None. **A.A. Keiser:** None.

Poster

PSTR287: Lifestyle, Physiological, and Molecular Modulators of Hippocampal Memory Function

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR287.18/KK65

Topic: I.07. Long-Term Memory

Support: SECIHTI
VIEP-BUAP 2026

Title: Exposure to bisphenol A during gestation and lactation periods impairs short-term as well as long- term memory in adult female low-yawning rats.

Authors: *H. AQUINO[1], C. CORTES[2], J. R. EGUIBAR, Sr.[3];
[1]Benemerita Univ. Autonoma de Puebla, Heroica Puebla de Zaragoza, Mexico; [2]Inst. of Physiol., B. Univ. Autonoma de Puebla, Puebla, Mexico; [3]Behavioral Neurophysiol., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico

Abstract: Memory disorders had been increasing systematically in the world and it is expected that worsen due to high anxiety levels and due to higher pollutant exposure. Plastic production oscillates between 4 and 8 megatons per year, with a growing tendency which is driven by the high demand for different industrial purposes. Approximately 70% of this plastic is used to manufacture polycarbonate and the production of epoxy resins and container coatings. For example, bisphenol A (BPA) is a synthetic plastic found in food and drink containers, then the ingestion happens regularity in lifespan. In fact, the BPA effects have been associated with cognitive impairments, including deficits due to its endocrine-disrupting mechanisms. In our laboratory, it has been shown that low-yawning (LY) rats are more anxious compared to high-yawning (HY) rats in different psychobiological tests. The aim of this study was to evaluate the effect of gestational and lactational period exposure to BPA in HY and LY female rats using the novel object recognition (NOR) test made between 0800 and 1000. We evaluated 31 HY and 30 LY female rats, which were maintained under standard conditions and following Mexican rules for care of laboratory animals and ARRIVE 2.0. BPA was administered through drinking water at a dose of 250 µg/Kg/day during the gestation and lactation periods. The litters were culled to 4 male and 4 female, maintained until 90 ± 2 postnatal days and then we evaluated the memory using NOR test. We observed an impairment in the short-term ($P<0.001$) and long-term ($P<0.001$) memory in LY female rats with the lower recognition index with respect to that obtained in HY female rats. In conclusion, gestational and lactational exposure to BPA causes an impairment in the short- and long- term memory in the high-anxious LY subjects, and female HY subjects are less affected. These results support that anxiety levels interact with this plastic-derived endocrine disruptor and it is capable to impair memory. So, it is important to reduce the exposure to plastic pollutants.

Disclosures: H. Aquino: None. **C. Cortes:** None. **J.R. Eguibar:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.01/LL1

Topic: I.08. Learning and Memory

Support: Institute for the Brain and Cognitive Sciences (IBAC)
Peter and Carmen Lucia Buck (PCLB)
Holster Scholars Program

Title: Subjective Time Estimation in Rats: Seconds to Minutes

Authors: *A. S. CHRISTENSEN, Jr[1], E. BERI[2], B. PIERRE PHILIPPE[3], G. LAURETANO[3], E. J. MARKUS[2], A. SADINSKY[3], S. KAMMA[3];
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Abstract: Time perception is a crucial aspect of life, influencing how humans organize daily activities, and task completion. However, time estimation is important for multiple survival-related variables from short term timing of movements, through longer term pacing of behavior and even longer-term resource management. Importantly, the passing of time has been shown to be subjective, influenced by a variety of outside factors (Eagleman, 2005). One method for measuring biases in the perception of time is the temporal bisection task (Church & Deluty, 1977), which provides a measure of the degree to which an animal determines a stimulus to "feel" as a long or short interval. In the current pilot study, rats were trained to respond to short and long duration light cue, followed by intermediate (probe) durations. The subjects' short/long categorization of the intermediate intervals indicated their bias in the long or short direction. In the first phase of the experiment, time estimation of a few seconds was examined. Animals were trained on a range of 2-8, 3-6 or 4-12 sec. In all three groups they were first trained to respond differently to the short (2, 3 or 4 sec) and long (8, 6 or 12 sec) duration light cue. This was followed by intermediate probes distributed symmetrically around the middle of the range (5, 4.5 or 8 sec respectably). Most animals showed a bias for treating the intermediate intervals as long. The shape of the function varied, some showing a more linear response while others showed more of a step function. In the second phase of the experiment, time estimation of minutes was examined. To date, the temporal bisection has used intervals of seconds or less. Animals were trained on a range of 60-120 sec. While it was considerably more difficult for our rats to learn the minute task, after extensive training this was possible in some animals. One objective of this study is to compare the biases and shape of the time estimation function for short (sec) and long (min) intervals within the same animal. The results may indicate different underlying systems for processing episodic time.

Disclosures: A.S. Christensen: None. **E. Beri:** None. **B. Pierre Philippe:** None. **G. Lauretano:** None. **E.J. Markus:** None. **A. Sadinsky:** None. **S. Kamma:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.02/Web Only

Topic: I.08. Learning and Memory

Support: SECIHTI 1269044

Title: Reinforcement uncertainty modulates the use of timing and working memory during the Midsession Reversal Task (MSR) in mice.

Authors: *A. OROZCO COLES[1], T. V. CAMPOS ORDONEZ[2], J. BURITICÁ[3];
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Abstract: Temporal control refers to situations in which behavior is regulated by temporal relations among environmental events. In the Mid-Session Reversal Task (MSR), performance may be controlled by both local cues derived from the outcome of the previous trial and temporal cues associated with session duration. Because reinforcement uncertainty reduces the reliability of local cues, greater reliance on temporal cues may be expected to anticipate contingency reversals. The present study evaluated how reinforcement uncertainty affects temporal control in a MSR task. Eight male CD1 mice were assigned to one of two groups: a fixed reversal with continuous reinforcement condition (F100) or a fixed reversal with 50% probabilistic reinforcement (F50); certain vs uncertain feedback. Subjects were exposed to 50 training sessions consisting of 50 trials each, in which the contingency reversal occurred at trial 25 for both groups. Training sessions were conducted with an 8s intertrial Interval (ITI). Following training, subjects were exposed to two test sessions with a 16s ITI. Results revealed evidence of mixed strategies. Analysis of solving strategies suggested that behavior was simultaneously controlled by temporal and local cues. In addition, PSE ratios were lower in F100 (0.43) than in F50 (0.73), suggesting a more pronounced temporal shift in the F100 condition. Although some subjects exhibited PSE ratios close to the value predicted by the temporal control hypothesis (0.50), the uncertainty introduced in F50 did not produce the expected increase in reliance on temporal cues or in the use of a timing strategy. These preliminarily findings suggest that reinforcement uncertainty does not increase reliance on temporal cues and that adaptation to contingency changes in the MSR task emerges from the integration of multiple sources of information.

Disclosures: A. Orozco Coles: None. **T.V. Campos Ordonez:** None. **J. Buriticá:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.03/Web Only

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)

Title: Acquisition of multiple timing priors without experimentally imposed behavioral contexts in a virtual batting task

Authors: *J. SUZUKI[1], T. IWANAGA[2], M. MIYAZAKI[1,2], T. KIMURA[3];
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Abstract: To optimize sensorimotor behavior in daily tasks involving multiple events (e.g., fastballs and slowballs in ball games), the brain must acquire multiple prior distributions of the events. Previous psychophysical studies have demonstrated that the brain can acquire two distinct prior distributions based on the differences in behavioral contexts in timing tasks. For example, in timing tasks with the dominant-hand keypress, two independent priors were effectively acquired by executing a concomitant motor response (nondominant-hand, foot, or vocal response), selectively for one prior (Natsume et al., 2025, Tanaka et al., 2026). Notably, Zahno et al. (2026) reported that in a naturalistic task such as returning tennis serves, participants learned a bimodal prior distribution of serve locations, where there was no conditioning of behavioral contexts. In this study, we tested whether participants could concurrently acquire two distinct timing priors in a virtual batting task without conditioning behavioral contexts. Participants wearing a head-mounted display performed the virtual batting task without any body constraints. The time interval from the pitcher releasing the ball to the ball reaching home plate was randomly sampled from either the short (500-900 ms) or long (1000-1400 ms) prior distribution (i.e., fastballs or slowballs). Participants could hit the balls if their swings were correctly timed with the ball's arrival regardless of the bat swing trajectory. Each participant performed 240 trials of the task. They were divided into color-cue and non-cue groups. In the color cue group, the two priors were indicated by the color of the virtual pitcher (blue or red). We selected color cues because they are known to be ineffective for learning two opposing force fields or two distinct timing priors. In the non-cue group, the color of the virtual pitcher remained unchanged regardless of the prior distribution. In this study, the two priors were uniform distributions; therefore, participants in the non-cue group were exposed to a single wide uniform prior (500-1400 ms). The results indicated that the color-cue group acquired two independent priors, whereas the non-cue group did not. Thus, even without experimentally conditioned behavioral contexts, humans can learn multiple timing priors in a naturalistic task involving complex movements. However, voluntary behavioral contexts may emerge during such movements, even when they are not experimentally imposed. Future studies should therefore analyze movement kinematics and electromyographic activity during task performance.

Disclosures: J. Suzuki: None. **T. Iwanaga:** None. **M. Miyazaki:** None. **T. Kimura:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.04/LL2

Topic: I.08. Learning and Memory

Support: NIH R00MH118422
NIH R01MH129582
NSF GRFP
UCSF Discovery Fellowship

Title: Neural mechanisms underlying an internally generated metronomic action

Authors: *J. R. FLOEDER, B. WU, M. ZHOU, J. WAGNER-CARENA, J. A. DISANTO, D. A. BURKE, A. D. SANDERS, H. JEONG, A. TAYLOR, F. FAROUQ, A. MORSI, V. K. NAMBOODIRI;
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Abstract: Proper timing is critical for survival and healthy behavior, with disruptions in action timing and time perception seen in various psychiatric and neurological disorders. However, timed actions, particularly those that are fully uncued and internally generated, are challenging to study using animal models. To address this gap, we have developed a novel rodent behavioral paradigm called the metronomic task. In this task, head-fixed mice learn to lick "metronomically" at regular intervals (a period ranging from ~1.5 to 3 seconds) in the absence of sensory cues. As such, this task is highly valuable to study internally generated, temporally organized action sequences. Using this task, we found that optogenetic inhibition of either the dorsolateral striatum or nucleus accumbens caused the metronomic licks of the mice to be slower and less precise. While prior studies have largely focused on the role of the dorsal striatum in voluntary movement, these results revealed the involvement of the nucleus accumbens in spontaneous timed actions. This motivated us to investigate dopamine release dynamics in the accumbens using dLight fiber photometry in this task. Surprisingly, we found that dopamine levels dipped following each timed lick bout, despite licking being an operant action occasionally resulting in reward. Furthermore, the magnitude of these dopamine dips weakly, but significantly, correlated with the timing of the subsequent lick; such a fast timescale correlation between dopamine and ongoing movement is rarely observed. To test whether this correlation has a functional role, we optogenetically inhibited ventral tegmental area dopamine neurons; this significantly increased the average time between lick bouts, consistent with a causal role for dopamine in the timing of this internally generated action. We next used 2-photon calcium imaging in the nucleus accumbens and saw that neuronal activity patterns systematically scale with the interval duration between lick bouts, demonstrating that the accumbens encodes timing and not just actions. Ongoing work involves additional 2-photon calcium imaging to investigate whether D1 vs D2-type medium spiny neurons in the nucleus accumbens are differentially engaged in this task. Collectively, this work establishes the metronomic task as a powerful platform for investigating the neural mechanisms of internally generated timing and reveals an unexpected role of the nucleus accumbens in regulating action timing.

Disclosures: J.R. Floeder: None. **B. Wu:** None. **M. Zhou:** None. **J. Wagner-Carena:** None. **J.A. DiSanto:** None. **D.A. Burke:** None. **A.D. Sanders:** None. **H. Jeong:** None. **A. Taylor:** None. **F. Farouq:** None. **A. Morsi:** None. **V.K. Namboodiri:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.05/LL3

Topic: I.08. Learning and Memory

Support: University of San Diego, College of Arts and Sciences

Title: Examining the Role of the Hippocampus in an Operant Time Duration Discrimination Task in Rats

Authors: *L. KAZANJIAN[1], S. TAYLOR[1], Z. DORROS[1], J. B. HALES[2];
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Abstract: Awareness of elapsed time duration is crucial for accurate memory formation and provides important temporal context when planning future actions. While temporal cognition is disrupted in certain diseases, including Alzheimer's (Haj and Kapogiannis, 2016) and Parkinson's (Riesen and Schnider, 2001) disease, the underlying neuropathology is still being investigated. The discovery of time cells in the hippocampus and entorhinal cortex helped establish a neural basis for some aspects of time perception in primary memory structures in the brain (MacDonald et al., 2011; Gray et al., 2020). While time cell studies describe temporal categorization of a sequence of events, humans also register the duration of elapsed time during and between events. Multiple brain regions have been proposed to contribute to this higher-level temporal process, with evidence that motor and sensory systems also influence neural timing (Paton and Buonomano, 2018). To further understand the neural circuits and regions responsible for time perception, we developed an operant time duration discrimination (oTDD) task. Previous studies from our lab characterized the effects of hippocampal lesions (Sabariego et al., 2021) and medial entorhinal cortex lesions (Vo et al., 2021) on a time duration discrimination (TDD) task that involved rats navigating a modified figure-8 maze. In our current study, male and female rats were trained to discriminate between a 10s and 20s tone/light stimulus by pressing either a left or right lever to receive a reward. Once rats reached criterion performance of 90% correct (out of 50 trials) on two out of three consecutive days, they received either an excitotoxic hippocampal lesion or a sham lesion surgery. After a recovery period, rats were tested on the same task to investigate hippocampal involvement in discriminating time duration. Preliminary results suggest that the navigational TDD task can be successfully adapted into an operant version, with rats reaching criterion performance in fewer days of training (than reported in Sabariego et al., 2021). Further analyses will examine differences in performance based on lesion and sex and will be compared to previous results using the navigational TDD paradigm. The oTDD paradigm presents several advantages over the previous TDD task, including faster training to criterion and

fewer experimenter interactions with rats during testing. The oTDD task can be easily adapted for a range of manipulations and has the potential to serve as a foundational paradigm for memory and neurodegenerative disease research.

Disclosures: L. Kazanjian: None. **S. Taylor:** None. **Z. Dorros:** None. **J.B. Hales:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.06/Web Only

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)

Title: Lead-in and follow-through motor responses with one hand facilitate multiple-prior acquisition in timing behavior with the other hand

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Abstract: In daily tasks, we encounter multiple events with different temporal statistics (e.g., fastball/slowball in ball sports). To optimize timing behavior in natural environments, the brain must learn and retain multiple prior distributions. Recent studies have shown that concomitant motor responses can facilitate the acquisition of multiple priors in timing tasks (Natsume et al., 2025; Tanaka et al., 2026). For example, when performing a task requiring a dominant hand response, participants acquire two independent priors more effectively when a secondary response with another effector (e.g., the nondominant hand or foot) is selectively paired with one prior. However, in natural behavior, accompanying movements often precede or follow the primary action (e.g., leg kicks precede bat swings in baseball). Moreover, previous studies have shown that lead-in and follow-through arm movements can serve as contextual cues that enable the learning of two opposing force fields (Howard et al., 2012, 2015; Gippert et al., 2023). Here, we investigated whether lead-in and follow-through motor responses with the nondominant hand facilitate multiple-prior acquisition in a dominant-hand timing task. Participants were presented with three sequential visual stimuli (S1, S2, and S3). S1-S2 and S2-S3 intervals were identical within each trial. Participants attempted to press a key to coincide with the onset of S3, with their dominant index finger. The stimulus intervals were sampled from either a short (450-1050 ms) or long (1200-1800 ms) prior distribution. The two priors were associated with different stimulus colors (green or orange) and alternated across trials. Participants selectively pressed another key with their nondominant hand for one of the colors (i.e., one of the priors) in addition to the primary timing response with their dominant hand. They were divided into two groups. In the lead-in group, the additional nondominant-hand response preceded the primary timing response.

In the follow-through group, this additional response followed the primary timing response. Both groups acquired two independent priors, as indicated by a longer acquired prior mean under the long prior than under the short prior. Moreover, in the lead-in group, the divergence between the acquired prior means was significantly greater than that previously observed under a concomitant-response condition (Tanaka et al., 2026), whereas no such enhancement was observed in the follow-through group. These results suggest that a preceding motor context more effectively facilitates the acquisition of multiple timing priors.

Disclosures: R. Takaki: None. **Y. Tanaka:** None. **N. Roach:** None. **M. Miyazaki:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.07/Web Only

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)

Title: Behavioral-context dependency between generalization and motor specificity in learning two distinct timing priors

Authors: *T. INAGAKI[1], Y. OKUMURA[1], N. W. ROACH[2], M. MIYAZAKI[1,3];
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Abstract: To apply Bayesian estimation to daily tasks including diverse events, the brain must learn and retain multiple prior distributions. Recent studies have revealed how multiple timing priors are acquired. For example, when participants respond using only a manual keypress across short and long prior distributions, they acquire a single prior by generalizing over the two distributions (“generalization”); then, they gradually acquire two independent priors after extensive training. In contrast, participants quickly acquire two independent priors when using distinct motor responses (keypress and vocalization), each paired with one prior (“motor specificity”). The present study examined whether previous learning under a condition that promotes generalization influences subsequent learning under a condition that promotes motor specificity, and vice versa. Each participant performed 640 trials of a coincidence timing task, in which stimulus intervals were sampled from either a short (450-1050 ms) or long (1200-1800 ms) distribution. The two priors were cued by the stimulus location (left or right of fixation). In Experiment 1, participants responded only by a dominant-hand keypress during trials 1-320 and then responded either by keypress or vocalization (“Ba”) according to the priors during trials 321-640. In Experiment 2, participants first responded by keypress or vocalization (trials 1-320) and then responded only by keypress (trials 321-640). The generalized prior acquired in the first half of Experiment 1 rapidly transitioned into two independent priors following the introduction

of motor-specific responses. Conversely, the two independent priors acquired in the first half of Experiment 2 rapidly changed to a generalized prior after the task switched to a single manual response. These results suggest that the expression of generalized and independent priors is highly dependent on the behavioral context in which they are acquired and tested. Interestingly, a difference between the experiments was also observed during the single-effector condition. A small, non-significant divergence between the acquired short and long priors was observed when participants initially responded only by keypress (Experiment 1). In contrast, no such divergence was observed when participants responded only by keypress after first acquiring two independent priors (Experiment 2). Although preliminary, this pattern suggests that previous learning under motor-specific conditions may alter subsequent learning dynamics when the task is later performed using a single motor effector.

Disclosures: T. Inagaki: None. **Y. Okumura:** None. **N.W. Roach:** None. **M. Miyazaki:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.08/LL4

Topic: I.08. Learning and Memory

Support: BrainWorks at the Center for Neurocognition and Behavior in the Wu Tsai Institute, Yale University (RRID: SCR_024556)

Title: Temporal context modulates neural dynamics during face perception

Authors: *L. GAO[1], I. ECHEVERRIA-ALTUNA[1,2], G. MCCARTHY[1], A. NOBRE[1]; [1]Psychology, Yale Univ., New Haven, CT; [2]Basque Ctr. on Cognition, Brain and Language, San Sebastián, Spain

Abstract: The dynamic external environment contains temporal regularities that help us anticipate when relevant events are likely to occur. A prevalent form of temporal regularity is rhythm, in which events follow a constant, repeating temporal structure. Previous studies using simple auditory and visual stimuli have shown that rhythmic patterns exogenously entrain temporal attention, prioritizing processing at expected moments in time over unanticipated ones. In this study, we explored how incidentally learned temporal rhythms guided temporal attention and influenced the processing of more complex, visual face stimuli.Twenty-one healthy participants viewed briefly presented faces (100 msec each) from the Chicago Face Database while undergoing magnetoencephalography (MEG). Their task was to respond as quickly and accurately as possible whenever a pre-designated target face appeared. Targets appeared sparsely, on average once every eight faces, within a stream of repeated non-target faces. The target identity remained constant throughout the experiment, whereas the non-target identity changed on occasion to define separate temporal contexts. Context duration was held constant at approximately 6 sec. Temporal expectations within the contexts were manipulated by varying the

inter-stimulus interval between faces. Intervals could be fixed (consistently short (500 msec) or long (1400 msec)) or variable (intermixed short and long). Reaction times (RT), accuracy and MEG signals were measured.Task performance for identifying the target face was highly accurate and did not differ between conditions. Consistent with previous findings, temporal expectations significantly improved RTs for targets at predictable short intervals compared to those appearing after short intervals in variable temporal contexts, but this benefit did not extend to predictable long intervals. Multivariate pattern analysis suggested that temporal context modulated the discriminability of neural face representations for both targets and standards, with differences emerging between predictable and unpredictable short-interval contexts. The findings highlight the role of temporal context in sculpting the neural representations during visual face perception.

Disclosures: L. Gao: None. **I. Echeverria-Altuna:** None. **G. McCarthy:** None. **A. Nobre:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.09/LL5

Topic: I.08. Learning and Memory

Title: Cognitive function: objective measures and subjective concerns in a continuous recognition task

Authors: J. CLIFFORD[1], C. B. ASHFORD[2], ***J. W. ASHFORD**[3], F. MOJABI[4], S. AKITT[4]; [1]Psychology, Col. of San Mateo, San Mateo, CA; [2]MemTrax, LLC, Redwood City, CA; [3]Psychiatry & Behavioral Sci., Stanford Univ., Palo Alto, CA; [4]WRIISC, Veterans Affairs Palo Alto HCS, Palo Alto, CA

Abstract: Information Processing models (IPMs) describe events that occur in the brain to process, encode, store and retrieve environmental stimuli. Such stimuli interact with and automatically engage processes in sensory memory (SM) and short-term memory (STM) which integrate and distinguish stimuli from other items in SM and STM and can consolidate information into long-term memory (LTM). These processes can be measured objectively by a continuous recognition task (CRT). However, individuals may have concerns about the adequacy of their own information processing capabilities (IPC).
Behavioral metrics gathered from a convenience sample of 18,178 unique individuals (male; 5,795; female; 12,383) aged 21-90 years old who performed an online CRT (MemTrax) of their learning, memory and cognition was used to quantify their IPC. This CRT presents 25 visual stimuli and 25 repeat stimuli in a series to participants instructed to attend to all stimuli and detect repetitions. To satisfy these task demands the stimulus on each trial must be compared by processes directed as instructed by those operations in working memory (WM) with the representations in STM of stimuli presented on previous trials until a match is or is not detected.

In this CRT, there are four possible responses to a stimulus: 1: correct rejection (correct analysis of an initial presentation of a stimulus produces a non-response); 2: HITs (correct recognition of a repeated stimulus produces a correct action response); 3: false alarm error (incorrect analysis of non-repeating stimulus produces an incorrect action response); or 4: miss error (incorrect analysis of a repeated stimulus produces an incorrect non-response). Response time (RT) is the average of responses to HITs.
Results show in this sample that females aged 45 to 65 years old outnumbered males in this age range by over two-fold and had over three-times the number of concerns about their memory than males. However, both groups produced similar behavioral metrics during the CRT. Response times for hits in those with memory concerns increased on trials with increasing numbers of misses, indicating inadequate IPC activation for correct responses as age progresses. Further, RT for hits remained stable with increasing numbers of false alarms, suggesting dysfunction in a separate component of the IPM system. Concerns about decline in intellectual function may reflect awareness of changes that occur with age during sensory and cognitive processes that are measured during CRTs. The present results suggest clinicians may use such metrics to quantify and distinguish patient concerns.

Disclosures: J. Clifford: None. **C.B. Ashford:** Other; CEO MrmTrax, LLC. **J.W. Ashford:** Other; Unpaid consultant to MemTrax, LLC. **F. Mojabi:** A. Employment/Salary (full or part-time):; THE DEPARTMENT OF VETERANS AFFAIRS. **S. Akitt:** A. Employment/Salary (full or part-time):; THE DEPARTMENT OF VETERANS AFFAIRS.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.10/LL6

Topic: I.08. Learning and Memory

Support: R01NS137650

Title: Distinct Thalamic Nuclei Orchestrate the Activity of Distinct Neuronal Populations within the Human Hippocampus During Memory Retrieval

Authors: *W. HUANG, J. PARVIZI;
Stanford Univ., Stanford, CA

Abstract: To date, our understanding of interactions between the hippocampus (HPC) and the thalamus in the human brain remains limited. In this study, we recorded from anterior (ANT, N=47) and pulvinar (PLV, N=56) nuclei and HPC (N=94) in 12 participants implanted with stereo-electroencephalography (sEEG) electrodes during a verbal memory task involving abstract and concrete words. ANT and PLV showed similar memory-related high-frequency activity (HFA) but opposing low-frequency (LFA) patterns, each mirroring HFA dynamics across two distinct HPC sites. Importantly, HPC-ANT coordination preceded HPC-PLV

interactions. Electrical stimulation provided causal evidence for distinct electrophysiological connectivity between HPC sites and the two thalamic subregions. Our findings provide direct evidence that human verbal memory relies on distinct, causally connected, frequency and time specific parallel hippocampal-thalamic networks.

Disclosures: W. Huang: None. **J. Parvizi:** None.

Poster

PSTR288: Timing and Temporal Processing

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.11/LL7

Topic: I.08. Learning and Memory

Title: The Role of Video Game Practice in Trial-by-Trial Adaptation, Consolidation, and Reinforcement Learning Biases

Authors: *L. LLAMAS-ALONSO[1], A. QUEVEDO-CALDERON[2], S. QUIÑONES BELTRAN[1], A. Q. ANGULO-CHAVIRA[3];
[1]Pyschology, [2]Univ. Autónoma de Baja California, Ensenada, Mexico; [3]Pyschology, Univ. Nacional Autònoma de Mèxico, Guadalajara, Mexico

Abstract: This study examined whether habitual video game play influences reinforcement learning dynamics, feedback adaptation, consolidation, and motivational learning biases. Seventy-two young adults participated, including 36 habitual gamers and 36 non-gamers matched on impulsivity and sensitivity to reward and punishment. Participants completed a gamified adaptation of the Probabilistic Selection Task (PST), which assessed reinforcement learning across learning, test, and transfer phases under probabilistic feedback contingencies (80/20, 70/30, and 60/40 reward schedules).Mixed-effects modeling revealed significant learning improvements across blocks ($z = 5.66$, $p < .001$), with gamers showing differential learning trajectories under higher uncertainty conditions, particularly for the most ambiguous stimulus pair (E/F; $z = -2.66$, $p = .008$). Win-Stay/Lose-Shift analyses indicated greater sensitivity to accumulated rewards in gamers ($z = 3.07$, $p = .002$), suggesting stronger trial-by-trial reinforcement integration. Exploration-exploitation analyses further showed that gamers displayed significantly lower exploration rates ($z = -2.19$, $p = .028$), reflecting a more exploitative decision policy throughout learning.During the test phase, gamers demonstrated higher overall accuracy ($z = 1.99$, $p = .047$), especially for the most difficult stimulus pair (E/F; $z = 2.80$, $p = .005$), suggesting enhanced consolidation of probabilistic value representations when feedback was removed. However, no significant group differences emerged in transfer-phase approach/avoidance biases, valence learning bias index scores, or inverse temperature (β) parameters. These findings suggest that habitual video game experience enhances dynamic feedback integration and adaptive learning under uncertainty, without altering stable motivational reinforcement learning biases.

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Poster

PSTR288: Timing and Temporal Processing

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.12/LL8

Topic: I.08. Learning and Memory

Support: R01 MH123069

Title: Temporal Linking of Contextual Fear Memories in Humans: A Virtual Reality Test of the Shared Ensemble Hypothesis

Authors: *S. Y. PATEL[1], D. SCHILLER[2], A. RADULESCU[3];
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Abstract: Fear generalization, the spread of conditioned fear to safe contexts, is a hallmark of anxiety disorders, yet its temporal determinants in humans remain poorly characterized. Research with Rodents demonstrate that memories encoded close in time share overlapping neural ensembles, rendering them susceptible to affective linking (Cai et al., 2016). We tested whether a shorter interval between encoding two distinct neutral virtual contexts promotes subsequent generalization of conditioned fear from one context to the other. Adults (n=32) were randomly assigned to a Near (~2-hour interval between Sessions 1 and 2) or Far (~2-day interval) group (n=16/group; groups matched on age and sex). Using an HTC Vive Pro 2 headset, participants explored three virtual apartments across four sessions: Apartment A (Session 1, neutral encoding), Apartment B (Session 2, neutral encoding), Apartment B again (Session 3, fear conditioning via animated zombie encounter), and Apartments A, B, and C (Session 4, test; C was a novel neutral context). Physiological responses including tonic Electrodermal Activity (EDA), Skin Conductance Response (SCR) amplitude, and Heart Rate (HR), along with self-reported arousal/valence and a source memory task were collected throughout. Fear conditioning was confirmed by a significant increase in tonic EDA during the zombie encounter relative to baseline exploration sessions (Repeated Measures ANOVA, p=.013). During Session 4, the Near group showed elevated self-reported arousal in Apartment A (M=4.66) comparable to the fear-conditioned Apartment B (M=4.53), while the Far group's Apartment A arousal returned toward their Session 1 baseline (M=3.87 vs. 3.90), consistent with context-specific fear retention (Cohen's d=0.47). Converging trends across SCR amplitude and HR difference indices (Test A minus Encode A) showed the same directional pattern, with the Near group exhibiting positive shifts and the Far group remaining near zero. Source memory mis categorization further supported this: the Near group showed a trend toward greater retroactive confusion of Apartment B items to Apartment A (B→A errors: Near M=1.33±2.23 vs. Far

M=0.75±1.22), while A→B errors were identical across groups (M=2.50, p=1.000), ruling out general memory impairment. These multi-modal converging trends provide proof-of-concept that the interval between context encodings modulates fear generalization in humans, with implications for understanding anxiety disorder development and optimizing the timing of exposure-based interventions.

Disclosures: S.Y. Patel: None. **D. Schiller:** None. **A. Radulescu:** None.

Poster

PSTR288: Timing and Temporal Processing

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR288.13/LL9

Topic: I.08. Learning and Memory

Support: JSPS KAKENHI (25H01096)
JSPS KAKEINHI (22K18263)

Title: Alternating and random presentation patterns of two timing priors reveal opposite influences of autistic traits on timing prior acquisition

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Abstract: Timing behavior can be optimized by integrating sensory signals with prior knowledge about temporal statistics. In everyday environments, the brain must learn and retain multiple prior distributions because different events often have distinct temporal characteristics. Previous work has shown that when short and long timing priors are presented alternately in a keypress timing task, participants initially generalize across the two distributions and later acquire two independent priors. In our recent study (Kimura et al., Neuroscience 2025), we investigated the effects of autistic traits on the learning of two timing priors in individuals with typical development. We found that the degree of divergence between the two acquired priors correlated positively with the Autism Spectrum Quotient (AQ) scores, suggesting that individuals with higher autistic traits more readily acquired separate priors. Autistic individuals often prefer predictable and repetitive behavioral sequences. Because alternating presentation creates a highly predictable sequence, the present study examined whether this relationship depends on the temporal structure of the environment. Participants viewed three sequential visual stimuli (S1, S2, and S3) presented at the center of a display, with identical S1-S2 and S2-S3 intervals on each trial. Based on the S1-S2 interval, participants attempted to press a key to coincide with the onset of S3, using only their dominant index finger. Stimulus time intervals were randomly sampled from either short (450-1050 ms) or long (1200-1800 ms) prior

distributions. Rather than alternating between the two priors conditions, presentation order was randomized and stimulus color (orange or green) was used to cue the relevant prior distribution. Each participant completed 640 trials of the task. The results contrasted with our previous findings. The degree of divergence between the two acquired priors negatively correlated with the AQ scores in trials 1-320, although it was non-significant in trials 321-640. Thus, in the early half of trials, individuals with lower autistic traits began to learn two independent priors whereas those with higher autistic traits continued to rely on a generalized prior. Together with our previous findings, these results suggest that individuals with higher autistic traits may be better able to segregate distinct timing statistics when they occur within predictable temporal patterns, whereas this advantage is reduced or reversed when the patterns are unpredictable.

Disclosures: K. Kimura: None. **N. Roach:** None. **M. Wada:** None. **M. Miyazaki:** None.

Poster

PSTR289: Language: Acquisition, Usage, and Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.01/LL10

Topic: I.11. Language

Support: Samuel F. Hulbert Endowed Chair Grant

Title: Electroencephalographical frequency characteristics of lexical retrieval during semantic verbal tasks and sentence formulation tasks

Authors: *A. W. CHIU, A. K. KIRK;
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Abstract: Speech and language impairments are estimated to affect 10-12% of the global population. This study aimed to investigate the EEG frequency characteristics during a structured speech-production task involving varying linguistic and motoric demands on individuals with speech impairments and non-native English speakers. Electroencephalography (EEG) data were collected from 21 college-aged participants (five of which were self-reported as having a speech impediment; seven were self-reported as non-native English speakers) as they completed the Boston Naming Test (BNT), in which subjects verbally identified images and formulated sentences using the identified objects. EEG signals were recorded using an OpenBCI system. We evaluated the relationship between the time delays in lexical retrieval, and the complexities of the words and sentences. We also examined the EEG signal powers at the theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30Hz) frequency bands between the Formulation phase and the Expression phase of sentences. A strong positive correlation was found between word complexity and response delay ($r = 0.82$, $p < 0.001$), indicating that increased lexical difficulty was associated with longer sentence-generation times. Alpha EEG band power was greater in the formulation phase than in the expression phase at the left temporal region ($p < 0.01$) related to anticipatory semantic preparation and lexico-semantic access of highly visual nouns in our image

bank. Unlike previous works dealing with EEG analysis of sentence comprehension, it suggested different mechanisms for the formulation and expression phrases of retrieval that did not exhibit direct correlations to word and sentence complexity. Our results suggested a possible neural suppression mechanism or active preparation in the subjects. There was little to no correlation between word and sentence complexity and any of the frequency band powers.
When separating the subjects with speech impediment from those without, our data showed a slight increase in the alpha frequency range. Since the alpha band had been reported to handle functional inhibition and the allocation of attentional resources during semantic anticipation during the formulation phase, subjects with speech impediment appear to require more cognitive efforts to achieve the tasks.

Disclosures: A.W. Chiu: None. **A.K. Kirk:** None.

Poster

PSTR289: Language: Acquisition, Usage, and Disorders

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Program #/Poster #: PSTR289.02/LL11

Topic: I.11. Language

Title: Survival Pressure as a Necessary Condition for Semantic Grounding in Coupled Sensorimotor-Linguistic Systems

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Abstract: The symbol grounding problem asks how symbols acquire intrinsic meaning. Harnad (1990) proposed a hybrid architecture grounding symbolic representations in iconic and categorical sensorimotor representations. Empirical tests of this framework through Evolutionary Language Games (Steel 2012) demonstrated that task-pressured agents can develop functional coordination signals, but the resulting proto-languages fail to generalize compositionally and do not scale to novel environments — suggesting sensorimotor grounding alone is insufficient. While recent multimodal approaches extend grounding through richer perceptual coupling (Kadambi et al. 2026), enactivist accounts argue that sensorimotor coupling alone is insufficient without genuine survival stakes (Di Paolo 2005; Froese & Ziemke 2009). Here we test this using a continuous-time recurrent neural network (CTRNN) navigating a 2D chemotaxis environment under metabolic constraints, coupled to a frozen large language model (LLM) prior. Rather than building symbolic structure from scratch, the LLM provides pre-existing compositionally organized semantic structure encoding global food distribution inaccessible to local sensors. Two conditions are compared: Condition A (no metabolic decay) and Condition B (survival pressure — lethal energy decay). Representational Similarity Analysis (RSA) measures alignment between CTRNN hidden state geometry and the LLM embedding space across training. Linear probing of hidden states tests whether agents implicitly represent semantic structure beyond what

motor outputs express. Results indicate that RSA alignment is significantly higher in Condition B than Condition A. Furthermore, linear probing reveals that hidden states in Condition B contain implicit semantic structure exceeding what is strictly required for task performance. These findings demonstrate that survival pressure drives the internalization of pre-existing semantic organization, as was discussed in Searle's Chinese Room. Finally, we discuss conditions for grounding in sensorimotor-linguistic systems referring to neural mechanisms of embodied cognition.

Disclosures: K. Ariga: None. **S. Yoshizawa:** None. **K. Mogi:** None.

Poster

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Topic: I.11. Language

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Title: The role of medial temporal lobe circuitry in age-related word comprehension declines: behavioral, anatomical, and genetic evidence

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Abstract: Word comprehension is essential for language. However, exactly how word comprehension is impacted in aging, and the neurobiological bases of any changes, are still not well understood. We present converging behavioral, neuroanatomical, and genetic evidence supporting the hypothesis that word comprehension in aging is impacted by age-related changes to medial temporal lobe (MTL) circuitry—in particular gray and white matter related to the hippocampus and rhinal cortex, well-studied learning and memory structures not traditionally implicated in language. Healthy adults (N=169, aged 18-85, 113 women) performed a word

comprehension (word-picture matching) task and underwent structural MRI scanning and genotyping of *APOE* and *BDNF* polymorphisms known to impact the MTL. Evidence revealed the following. First, accuracy and response time (RT) performance declined, especially for words learned later in life (which should rely more on the MTL than earlier-learned words because they have undergone less systems consolidation). Second, these declines were mediated most reliably by metrics of MTL-related structures, especially white matter integrity of key tracts projecting to the rhinal cortex, namely the inferior longitudinal fasciculus and a subsection of the cingulum bundle which projects to the rhinal cortex. Hippocampal volume and associated white matter (i.e., fornix) integrity, in addition to certain neocortical metrics (volumes of temporal pole, middle temporal cortex, superior parietal cortex, anterior cingulate cortex, and inferior frontal cortex, as well as inferior fronto-occipital fasciculus integrity) also mediated these age-related declines. Third, carriers of alleles linked to detrimental MTL outcomes (*APOE* ε4 and *BDNF* Met) showed steeper declines than non-carriers. This comprehensive hypothesis-driven study elucidates the "what" and "why" of word comprehension changes in aging and specifically links declines to the MTL. The results have translational ramifications for word comprehension in Alzheimer's disease (in which rhinal and hippocampal circuitry are affected), and basic-research implications for both language and the MTL—including how the latter underlies the former. The study demonstrates that linking language to well-studied brain structures not generally viewed as language-related can substantially advance our understanding of this critical human capacity.

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Poster

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Topic: I.11. Language

Support: This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan, Grant No. BR27198099

Title: Behavioral markers of cognitive control during multilingual language processing in Kazakh-Russian-English trilinguals

Authors: *K. ZHAKSYLYKKYZY, Z. IBRAYEVA, A. KUSTUBAYEVA, M. ZHOLDASSOVA;
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Abstract: Multilingual speakers must select task-relevant lexical information while managing competition from non-target languages, a key issue in the cognitive neuroscience of language control. Multilingual processing models predict that language accessibility varies with dominance, acquisition sequence, and learning history. Kazakh-Russian-English trilinguals are a

valuable test case because Kazakh and Russian differ typologically and sociolinguistically, while English is acquired later. This study tested whether Stroop interference is language-sensitive in this underrepresented population. Twenty adult trilinguals participated, mean age=23.3 years, range=18-29; 9 female and 11 male: Kazakh-L1/Russian-L2/English-L3 and Russian-L1/Kazakh-L2/English-L3 speakers. Language background, acquisition sequence, daily use, and self-rated proficiency were assessed with the Language Experience and Proficiency Questionnaire (LEAP-Q); all participants met a minimum English criterion of IELTS 6.0 or equivalent. Participants completed a computerized Stroop task with standard color-word and semantic color-concept blocks. Kazakh, Russian, and English stimuli included congruent and incongruent trials as within-subject controls. Median reaction times (RTs) for correct responses and accuracy were analyzed using a mixed repeated-measures ANOVA with Block, Language, and Congruency as within-subject factors and L1 group as a between-subject factor. RTs showed a significant Stroop effect, with slower responses to incongruent than congruent trials, $F(1,18)=10.95$, $p=.004$, $\eta p^2=.378$. A significant Language × Congruency interaction, Greenhouse-Geisser corrected $F(1.69,30.48)=4.49$, $p=.024$, $\eta p^2=.200$, indicated that interference differed across languages. Interference was largest in Kazakh (72.91 ms), followed by Russian (32.64 ms) and English (27.65 ms). The Russian-L1 group was slower overall than the Kazakh-L1 group, $F(1,18)=5.77$, $p=.027$, $\eta p^2=.243$, but did not significantly modulate language-specific interference. Accuracy was high overall and showed no significant congruency effect. These preliminary findings suggest that trilingual Stroop interference is language-sensitive rather than uniform across Kazakh, Russian, and English. Because L1 group did not modulate the Language × Congruency effect, the larger Kazakh interference should not be interpreted as a simple L1-driven pattern. Instead, it may reflect variable Kazakh/Russian dominance, lexical automaticity, acquisition sequence, and differential inhibitory demands in multilingual language control.

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Poster

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Topic: I.11. Language

Support: NIDCD Grant R01DC020446-04

Title: Localization of pseudohomophone reading to frontoparietal operculum reveals importance of orthography-to-phonology-mapping in pseudoword reading deficits

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Abstract: Phonological reading deficits are the most common type of acquired reading deficits, diagnosed based on difficulty reading unfamiliar, meaningless, but pronounceable letter strings (pseudowords; PSWs) compared to real words. Deficits in PSW reading may arise due to difficulty mapping a novel orthography to phonology (OPM) or in assembling a novel motor plan for production (phonological assembly; PA). Multivariate lesion-symptom mapping (LSM) studies have localized PSW reading deficits to frontoparietal opercular regions often implicated in speech production, but it remains unclear whether these lesions relate primarily to deficits in OPM or PA. Here, we test this question by examining the reading of pseudohomophones (PSH), novel letter strings that are pronounced like known words with stored phonological motor plans (e.g. hoap). Word, PSW, and PSH reading accuracy along with structural MRI scans were collected in a large sample of left hemisphere stroke survivors (n=67, M age=58.82yrs, 33 female/35 male) and controls (n=65, M age=59.32yrs, 33 female/32 male). To identify regions involved in novel OPM, we performed separate LSM analyses for PSW controlling for words, and PSH controlling for words, as well as a conjunction analysis on these two maps. To identify regions involved in PA, we performed an LSM analysis for PSW controlling for both PSH and words. All analyses included covariates of age, education, and lesion size. Significance was tested using 5000 permutations (voxelwise $p<.005$, clusterwise FWE $<.05$). Repeated measures ANOVA was used to examine stimulus type, patient status, and interaction of the two. We found a significant main effect of patient status ($p<.001$) and an interaction of patient status and stimulus type with left hemisphere stroke survivors showing comparatively larger deficits reading both PSH and PSW ($p<.001$). LSM identified overlapping lesion clusters for both PSW vs. words and PSH vs. words, confirmed with the conjunction analysis (OPM analyses). These clusters involved the parietal operculum within the supramarginal gyrus, extending through the white matter to the frontal operculum in the precentral gyrus. The PA analysis showed no significant regions associated with deficits in PSW controlling for both PSH and words. The frontoparietal operculum is implicated in motor planning for speech, but these results suggest that during reading, these regions may be co-opted for OPM. Treatment to strengthen OPM may then be beneficial in improving phonological reading skills for people with acquired reading deficits.

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Poster

PSTR289: Language: Acquisition, Usage, and Disorders

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Program #/Poster #: PSTR289.06/LL15

Topic: I.11. Language

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

Title: Neural correlates of speech planning and production during stuttered speech in adults who stutter.

Authors: *N. KUMAR, C. ODERBOLZ, M. WILLIAMS, J. ORPELLA;
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Abstract: Stuttering is a neurodevelopmental communication disorder affecting over 70 million people worldwide. It is characterized by involuntary disruptions in speech fluency, including sound and syllable repetitions, prolongations, and articulatory blocks. Although prior studies have identified trait-level neural differences in adults who stutter (AWS), less is known about the state-dependent neural processes preceding and accompanying naturally occurring stuttering events. Here, we used fMRI together with a recently validated speech-production paradigm that leverages the ability of AWS to predict stuttering on specific words—allowing us to examine neural activity associated with speech planning and production of stuttered versus fluent utterances within the same individuals. Twelve AWS (mean age = 33.5 years; 4 female) completed a word-production task using individualized word lists composed of words likely to be stuttered or fluent. On each trial, participants produced visually-presented words following a controlled delay period, enabling separation of speech planning and production stages. The paradigm successfully elicited a balanced number of stuttered (μ= 47%; SD=±17) vs fluent trials across participants. Whole-brain fMRI data were analyzed using generalized linear models comparing stuttered and fluent trials. Statistical maps were thresholded at voxel-wise $p_{unc.} < 0.001$ with cluster-level correction ($p_{FWE} < 0.05$; minimum cluster extent = 20 voxels). During speech planning, stuttered relative to fluent productions were associated with increased activation in medial frontal regions, including the anterior/mid cingulate cortex and supplementary motor area (SMA/pre-SMA), as well as bilateral anterior insula/inferior frontal regions and right premotor cortex suggesting that stuttering-related neural differences emerge before speech onset, potentially reflecting altered preparation and initiation of speech. During speech production, stuttered speech was associated with broader recruitment of speech-related regions, including bilateral insula and inferior frontal/opercular cortex, cerebellum, cingulate cortex, SMA, precentral gyrus, supramarginal gyrus, and parietal regions suggesting increased demands on speech motor control during overt stuttering events. Prominent right-hemisphere involvement was observed in frontal opercular, premotor, and sensorimotor regions. These findings indicate that stuttering is associated with state-dependent alterations in neural systems supporting both speech planning and production.

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Poster

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Topic: I.11. Language

Support: GRAMMY Museum Grant AGR DTD 07-14-2023

Title: Music training differentially impacts neural responses to expectation in young adults with and without dyslexia

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Abstract: The brain's ability to generate and evaluate expectations of future events is important in daily skills, including music and reading. Deficits in auditory perception are reported in those with dyslexia, and prior work suggests musical training may improve reading in this population by improving the brain's ability to encode speech sounds or make predictions about letter-sound relationships. Thus, this study evaluated relationships among musical training, auditory perception, and expectation in young adults with dyslexia.Young adults (18-35 y/o) with (DYS; $n = 22$) and without (typically developing/TD; $n = 56$) dyslexia with varying musical experience completed an electroencephalography (EEG) music perception task to classify major or minor melodies. Event-related potentials (ERPs) associated with auditory processing and expectation were extracted from responses to the critical note at which the mode of each melody becomes unambiguous. Participants also completed a behavioral pitch discrimination task and a complex auditory categorization task assessing sensitivity to major and minor tone scrambles. Regression analyses examined relationships among years of musical training, task performance, and ERPs separately for each group.EEG data revealed that, for TD readers, greater musical training positively predicted LPC amplitudes to minor melodies ($\beta = 0.043$ μV, $t(54) = 2.28$, $p = 0.027$), replicating prior work by our group. In TD, years of musical training also showed trending negative associations with N1 amplitudes ($p = 0.070$) and trending positive associations with P2 amplitudes ($p = 0.085$). No relationships between musical training and ERP amplitudes were observed in DYS participants ($ps > 0.120$).Within the TD group, better complex auditory categorization, as indicated by higher d' on the tone scramble task, was associated with greater P2 amplitudes ($\beta = 0.09$ μV, $t(51) = 2.06$, $p = 0.044$) and greater LPC amplitudes to minor melodies ($\beta = 0.20$ μV, $t(51) = 3.13$, $p = 0.003$). No significant relationships were observed within the DYS group ($ps > 0.282$).Findings suggest that musical experience and pitch perception are associated with enhanced neural processing of musical expectation in TD readers, particularly during the LPC component linked to auditory expectation. The absence of similar relationships in DYS aligns with evidence that complex pitch perception deficits persist despite musical experience in dyslexia, suggesting musical training may be less effective at enhancing complex auditory categorization in this population. Further work is needed to identify mechanisms by which musical training improves reading subskills in struggling readers.

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Poster

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Topic: I.11. Language

Support: Institutional startup funds from Penn State College of Medicine to KS

Title: Predicting the meaning of real words from their speech acoustics: a machine learning approach

Authors: *J. DORSI[1], V. KUMAR[2], S. A. LACEY[1], L. NYGAARD[4], K. SATHIAN[3]; [2]Neurol., [3]Dept. of Neurol., [1]Penn State Col. of Med., Hershey, PA; [4]Psychology, Emory Univ., Atlanta, GA

Abstract: Speech iconicity refers to the idea that some words sound like their meaning. For example, “balloon” and “spike” are judged as sounding rounded and pointed, respectively. Prior work established relationships between phonemes and meaning: words with more rounded meanings tend to contain phonemes judged as sounding more rounded (Sidhu et al., 2021, Psychon B Rev). Judgments of roundedness and pointedness in pseudoword sounds can be accurately predicted by a k-nearest neighbors (kNN) algorithm using specific combinations of speech acoustic parameters (Kumar et al., 2025, J Acoust Soc Am). Building on this work, we applied a kNN algorithm to predict the rounded/pointed meaning scores (taken from Sidhu et al., 2021) of 160 real words, examining 12 speech acoustic parameters: the fast Fourier transform, spectral tilt, speech envelope, the fraction of unvoiced frames (FUF), the number of pulses, the harmonics-to-noise ratio, mean autocorrelation, the mean and SD of the fundamental frequency (F_0 & F_0SD), jitter, shimmer, and word duration. We iteratively tested every possible combination of these parameters for how well the predicted meaning scores correlated with actual meaning scores. We found that a combination of six acoustic parameters produced the most accurate predictions of word meaning ($r = .31$, $p < .001$). These parameters included measures of voicing (i.e., the FUF), the speech amplitude profile (i.e., speech envelope), and speech stability (i.e., jitter, shimmer, mean autocorrelation, and F_0SD). Notably, the FUF and shimmer also predict how rounded/pointed pseudowords sound (Kumar et al., 2025), suggesting a partially shared acoustic basis for real word meaning and judgments of pseudoword sound. In a post hoc analysis, a kNN model also accurately predicted perceived roundedness/pointedness estimated from phoneme composition ($r = .45$). The optimal parameter set in this analysis comprised eight parameters, including five of the same parameters as for the meaning prediction, with the exception of F_0SD. The convergence of these parameter sets points to shared acoustic features underlying both sound-based judgments and semantic associations, providing support for an acoustic foundation of speech iconicity.

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Poster

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Topic: I.11. Language

Support: SNSF Grant P500PS_225257
Joan Orpella Start-up Funds Georgetown University, Department of Neuroscience

Title: Quantifying information dynamics in speech perception

Authors: *C. ODERBOLZ, J. ORPELLA;
Dept. of Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: During speech perception, the brain transforms the speech signal into abstract linguistic representations. Prior work indicates that subregions of the left superior temporal gyrus (STG) encode representations of units such as phonemes, syllables, and words whereas the right STG represents prosodic units. These representations are organized hierarchically in ventral processing streams, becoming increasingly abstract from posterior to anterior STG. What remains unclear is how these representations emerge, i.e. *what* information is communicated and *how* that information contributes to computation. We address these questions using a novel information-theoretic approach to characterize information dynamics within the ventral language streams. We first validated this approach using fMRI data from a binaural integration task. An ambiguous consonant-vowel (CV) syllable was presented to the right ear, while a disambiguating cue (a high vs. low F3) was delivered to the left ear. Because identification of the CV syllable requires the integration of complementary acoustic features distributed across ears/hemispheres, this task allowed us to probe information dynamics within and across ventral streams. We find that the disambiguating feature is first processed *intra*-hemispherically in the right hemisphere, propagating from Heschl's gyrus to pSTG. Unique information from left and right pSTG is then integrated in *right* aSTG, consistent with the emergence of a unified speech percept. This information is then transmitted to the *left* anterior insula. These information dynamics strongly predicted listeners' behavior. Next, we quantified information dynamics in the right ventral stream. In previous work, we showed that fundamental frequency (f0) processing progresses from posterior, acoustic representations to anterior, abstract representations in the right STG. Listeners used these abstract representations to classify stimuli according to their sentence type (question vs. statement). Here, we show that speech perception meaningfully re-organizes information dynamics between the right pSTG and aSTG relative to resting state. We observe synergistic interactions in right aSTG, suggesting a role for this region in integrating information. Indeed, synergistic interactions increase along the posterior-to-anterior axis of the right STG, underscoring the hierarchical organization of the right ventral stream. These dynamics differ strongly between correct and incorrect trials, suggesting that they are critical for behavior. Treating information as a dynamic, decomposable entity provides insight into how complex cognition and behavior arise.

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Poster

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Topic: I.11. Language

Support: GUMC Start-up Funds

Title: Linking lysosomal-pathway mutations to persistent developmental stuttering

Authors: *J. ORPELLA, N. KUMAR, M. WILLIAMS, C. ODERBOLZ;
Dept. of Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Speech production depends on precise coordination of the speech-motor network. In persistent developmental stuttering (PDS), dysfunction within this network is thought to contribute to the blocks, prolongations, and repetitions that characterize the disorder. Recent evidence implicating lysosomal trafficking genes (*NAGPA, GNPTAB, GNPTG*) raises the possibility that genetically driven metabolic vulnerability contributes to dysfunction within the speech-motor network, where these genes are highly expressed. We test this hypothesis by assessing neural markers of metabolic vulnerability in adults who stutter (AWS; n = 15). Whole-exome sequencing was used to identify individuals carrying lysosomal-pathway mutations (AWSm+). We then recruited age- and sex-matched AWS without these mutations (AWSm−) and typically fluent controls (TFC; n = 15), allowing us to distinguish mutation-related effects from neural differences associated with stuttering experience or age. We quantified metabolite concentrations and cerebral blood flow (CBF) in the left inferior frontal gyrus (IFG) using MR spectroscopy and arterial spin labeling. If lysosomal-pathway mutations increase metabolic stress within high-energy-demand speech-motor circuits, the IFG may be particularly vulnerable given its role in planning, initiating, and sequencing speech programs. Although CBF measures and metabolite concentrations overlap between AWS and TFC, considering mutation status reveals meaningful within- and between-group differences. AWSm+ show decreased lactate concentrations in the left IFG compared to both TFC and AWSm−. Lactate contributes to brain energy metabolism and cerebral microcirculation. Similarly, N-acetyl-aspartate (NAA) indexes neuronal health, whereas creatine (Cr) supports ATP resynthesis. However, although NAA and Cr appear lower in AWSm+ than TFC, they do not differ relative to AWSm−. Left IFG perfusion is reduced in AWSm+ compared to AWSm− and TFC. This effect is regionally specific: AWS and TFC show comparable whole-brain perfusion. At the same time, AWS show delayed whole-brain blood arrival but faster delivery to the left IFG compared to TFC. Taken together, these neural markers indicate metabolic stress and reduced energy metabolism in AWSm+ within a critical region of the speech-motor system. These anomalies may reflect impaired cellular waste clearance and toxin buildup, consistent with recent animal model data.

Disclosures: J. Orpella: None. **N. Kumar:** None. **M. Williams:** None. **C. Oderbolz:** None.

Poster

PSTR289: Language: Acquisition, Usage, and Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.11/LL20

Topic: I.11. Language

Support: Becas Nacionales para Estudios de Posgrado CONAHCYT

Title: Pragmatics, prosody, and sexual innuendos in (Mexican) Spanish: exploring the neurocognitive bases of albur comprehension

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Abstract: Albur (plural albures) is a double entendre of sexual meaning, characteristic of Mexican Spanish, whose linguistic structure seems to be mainly based on calembour and polysemy. There are many prejudices concerning the comprehension and use of albur, as it is considered a phenomenon restricted to male speakers, and frequently associated to people from a low socioeconomic status and scarce access to education. Given its social status as taboo, currently there are almost no studies in the neurocognitive mechanisms of sexually evocative speech, and there are no previous works for any Spanish-speaking country. Given the above, we have designed an experimental paradigm to study the neurocognitive bases of albur, trough behavioral and fMRI techniques. Stimuli were constructed as short dialogues (two interventions each), for the albur stimuli, and two control conditions: sarcasm and literal language. The critical part (i.e. the part that gives rise to the double entendre) of the selected albures in the previous step were used to design the albur stimuli, sarcasm stimuli were adapted from previous works and literal language stimuli were designed to be similar to the other two categories in length and lexicon. In total, 75 stimuli were constructed (25 per category). Behavioral results of the pilot study reflected a high correct identification of the three categories (<70% overall): participants were able to accurately discriminate among the three conditions based solely on prosodic cues, even in absence of other contextual or extralinguistic features.Albur stimuli presented an acoustic profile different to literal language stimuli, with lower measures in fundamental frequency ($p = 0.0001392$), and amplitude ($p < 0.0001$). Given the acoustic differences, albur stimuli are perceived as produced with lower pitch and intensity with respect to literal language stimuli. Given that the pilot study has given the expected results, we will continue the project in two ways: 1) running the behavioral experiment with a bigger and more heterogeneous sample, and 2) running the fMRI experiment.The fMRI experiment will take place in the same manner as the behavioral experiment, with the participants having to assign the different audio recordings to the correct category. With the fMRI experiment, we expect to broaden the current knowledge on the neurocognitive basis of the processing of the emotional prosody related to certain indirect speech acts in general, as well as the brain processing of sexually evocative speech.

Disclosures: E. Ruiz Alanis: None.

Poster

PSTR289: Language: Acquisition, Usage, and Disorders

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR289.12/LL21

Topic: B.08. Epilepsy

Title: Striatal stimulation alters the distinctness of lexical representations and enhances word learning in humans

Authors: ***N. J. KILLIAN**[1], A. WILLIAMS[2], A. BORO[3], E. N. ESKANDAR[4];
[1]Neurosurg., [2]Albert Einstein Col. of Med., Bronx, NY; [4]Neurosurg., [3]Albert Einstein Col. of Med. - Montefiore Med. Ctr., Bronx, NY

Abstract: The neurophysiological mechanisms underpinning language learning are poorly understood, limiting our ability to treat disorders such as aphasia, which affects over 2 million people in the US, and for which there are no accepted pharmacological or neuromodulatory treatments. High-frequency stimulation in the nucleus accumbens (NAc) during stimulus presentation, followed by caudate (Cd) stimulation after correct responses, enhances associative learning rates (Katnani et al., 2016). We hypothesized that because language learning is associative, stimulation of these striatal regions may enhance the learning of foreign word - picture associations. Five epilepsy patients undergoing stereotactic electroencephalography (SEEG) monitoring performed a four-alternative forced-choice Swahili word-learning task with bilateral NAc+Cd stimulation (8 to 14 words per subject were learned over 240-330 trials). Stimulation improved learning rate within a single ~30-minute session with interleaved stimulated and unstimulated words (mean trials to criterion 6.3 vs 14.8 for NAc+Cd stimulated words vs. unstimulated words, mixed-effects beta=−5.74, $P = 0.003$). We then explored the potential mechanisms underlying the dramatic improvement in learning. We found that post-stimulation LTP-like plasticity developed across learning in the NAc during word reading and later in the Cd after correct-response feedback. These plasticity effects became stronger with learning for NAc+Cd stimulated words compared to unstimulated words ($P < 0.001$, Wilcoxon signed-rank test, n=31 stim., n = 23 unstim. words). Local field potentials (LFPs) during word reading, post-NAc stim, had distinct, well-separated trajectories. Whereas, unstimulated words clustered in a narrower manifold. Indeed, pairwise trajectory distances were up to 2.7x larger for stimulated words, and this distinctness was correlated with learning rate (Spearman's rho = 0.58, $p<0.001$). Interestingly, neither stimulation nor the changes in trajectory distinctness altered the anatomical flow of peak activity (Kendall's W, $p<0.001$ in N=5 of 5 subjects). Taken together, these results demonstrate that NAc+Cd stimulation reshapes the geometry of lexical representations in speech and language areas and accelerates word learning.

Disclosures: N.J. Killian: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder of Neuradaptive. **A. Williams:** None. **A. Boro:** None. **E.N. Eskandar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder of Neuradaptive.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.01/LL22

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

Title: Derivation and validation of germline-competent embryonic stem cells from immunodeficient NOG mice with targeted Tfrc humanization

Authors: M. L. JACOBSON[1], E. GOMAS[2], C. NIEMIETZ[2], C. RAYMOND[1], *S. R. STERLACE[1], J. R. RICHARDSON[1], P. SCHAUERTE[2], J. WELCKER[2];
[1]Taconic Biosci., Rensselaer, NY; [2]Taconic Biosci., Leverkusen, Germany

Abstract: Severely immunodeficient NOG mice support engraftment of human cells and tissues, but complex allele engineering in this background has been limited by the lack of germline-competent embryonic stem cells (ESCs). We conducted an exploratory study to derive, characterize, and genetically modify ESCs from NOG (NOD.Cg-PrkdcscidIl2rgtm1Sug/JicTac) mice and to establish feasibility for generating neuroscience-relevant humanized knock-in alleles. Blastocysts were isolated at 3.5 days post coitum and inner cell mass outgrowths were cultured on mouse embryonic fibroblast feeders in LIF/2i conditions. ESC lines were expanded, cryopreserved, and assessed for ploidy, sex, and pluripotency marker expression. Germline competence was tested by blastocyst injection. To demonstrate targeted engineering in this background, the endogenous mouse Tfrc locus was modified by humanized knock-in replacement of the extracellular domain with the orthologous human TFRC sequence, while retaining mouse transmembrane and intracellular domains. Targeted clones were evaluated by Southern blotting and ploidy analysis before blastocyst injection. Thirteen ESC lines were derived from 38 blastocysts; nine were validated for ploidy, sex, and pluripotency markers. Two of six tested ESC lines transmitted through the germline. Tfrc targeting in one ESC line yielded validated humanized TFRC knock-in clones; three targeted clones were injected, and one transmitted the humanized allele to the G1 generation. These data establish germline-competent ESCs from the NOG background and demonstrate that large, locus-specific humanized alleles can be generated directly in this immunodeficient strain. Humanized TFRC NOG mice may provide a platform for evaluating receptor-mediated blood-brain barrier drug delivery in an immunodeficient background, including studies that combine BBB-targeted therapeutics with human cell or tissue engraftment. This model context may be particularly relevant for neuroscience programs that require assessment of human-targeted BBB transport mechanisms alongside xenogeneic cell therapy approaches, human immune-cell engraftment, tumor xenografts, or other humanized tissue systems.

Disclosures: M.L. Jacobson: A. Employment/Salary (full or part-time):; Taconic Biosciences. **E. Gomas:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **C. Niemietz:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **C. Raymond:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **S.R. Sterlace:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **J.R. Richardson:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **P. Schauerte:** A.

Employment/Salary (full or part-time):; Taconic Biosciences. **J. Welcker:** A. Employment/Salary (full or part-time):; Taconic Biosciences.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.02/LL23

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

Title: AAVone2.1 Single-Plasmid Platform Achieving over 70% Full AAV Particles at Harvest and up to 1E16 VG/L Production Titers

Authors: Z. SHI[1], B. WANG[1], C. XU[1], D. YU[1], ***Q. WANG**[2,1];
[1]AAVnerGene Inc., Rockville, MD; [2]Wang, Rockville, MD

Abstract: Adeno-associated virus (AAV) vectors have emerged as leading platforms for in vivo gene delivery and genome editing and play a central role in the development of gene therapies for neurological disorders. However, current AAV manufacturing platforms based on triple-plasmid transfection (AAVtri) suffer from low productivity, poor batch-to-batch consistency, and a high proportion of empty capsids and DNA impurities. These limitations significantly increase manufacturing costs and restrict clinical scalability. Temporal, spatial, and quantitative mismatches between AAV genome replication and capsid protein synthesis are likely major contributors to the low productivity and low full-particle ratios commonly observed in conventional AAVtri systems. To address these challenges, we previously developed AAVone1.0, a single-plasmid AAV production system integrating adenoviral helper genes, AAV Rep/Cap genes, and the AAV vector genome into a single construct. By eliminating spatial mismatches among production components, AAVone1.0 significantly increased AAV productivity (2-4 fold versus AAVtri). However, it only modestly improved the percentage of full capsids at harvest, suggesting that temporal and quantitative imbalances remained major limiting factors. Here, we report the development of AAVone2.1, the second-generation AAVone platform, engineered to further optimize the coordination between AAV genome replication and capsid assembly. AAVone2.1 achieved greater than 70% full-particle ratios at harvest across multiple natural serotypes (including AAV1, AAV6, AAV8, AAV9, AAVrh.10, and AAVrh.74) as well as engineered capsids (such as AAV-DJ, AAVmyo, AAV-ShD, AAV-PHP.eB, and AAV-BI-hTFR1), while maintaining or further increasing the productivity achieved with AAVone1.0. Combined with process optimization, optimized transfection reagents (such as PEIone), enhancers, and engineered producer cell lines (such as HEK293one), the AAVone2.1 platform achieved crude production titers of up to 1 × 10^16 vg/L. Overall, the updated AAVone platform addresses both productivity and full-capsid limitations and represents a highly efficient, streamlined, cost-effective, and reproducible AAV manufacturing system. These properties make AAVone2.1 particularly well suited for scalable GMP-grade AAV vector production.

Disclosures: Z. Shi: None. **B. Wang:** None. **C. Xu:** None. **D. Yu:** None. **Q. Wang:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.03/LL24

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

Support: NIH UF1MH128339
NIH UM1MH130981
NIH P51OD010425
NIH U420D011123

Title: A Cross-Species Enhancer-AAV Toolkit for Cell Type-Specific Targeting Across the Basal Ganglia

Authors: *M. E. WIRTHLIN[1], S. SOMASUNDARAM[1], N. TASKIN[1], N. KEMPYNCK[2], M. SCHMITZ[1], E. THOMAS[1], M. HOOPER[1], Y. BEN-SIMON[1], X. OPITZ-ARAYA[1], J. K. MICH[1], A. OSTER[1], D. DWIVEDI[1], F. C. COLLMAN[1], N. DEE[1], T. S. MOLLENKOPF[1], K. SMITH[1], J. WATERS[1], I. ERSING[3], N. J. JOHANSEN[1], J. A. MILLER[1], H. ZENG[1], E. S. LEIN[1], Y. KOJIMA[4], G. D. HORWITZ[5], B. P. LEVI[1], T. L. DAIGLE[1], B. TASIC[1], T. E. BAKKEN[1], J. T. TING[1];
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Abstract: The mammalian basal ganglia (BG) orchestrate motor control, reinforcement learning, and action selection, and their dysfunction is implicated in a host of neurological and psychiatric disorders. Despite advances in defining BG cell type diversity through transcriptomic, anatomical, and physiological characterization, precise genetic access has remained limited beyond canonical spiny projection neurons (SPNs) and beyond the mouse, with major nuclei including the pallidum, subthalamic nucleus (STN), and dopaminergic midbrain broadly lacking experimental tools for cell type-specific perturbation in non-human primates. To ameliorate this, we developed the Cross-species Enhancer Ranking Pipeline (CERP), which integrates single-nucleus RNA-seq and ATAC-seq from mouse and macaque, mapped to the Human and Mammalian Brain Atlas consensus BG taxonomy, to prioritize enhancer candidates by chromatin accessibility, evolutionary conservation, and sequence modeling. Candidate enhancers were cloned into AAV vectors and screened in mouse via systemic retro-orbital delivery, with promising candidates advancing to cross-species validation by stereotaxic injection in macaque. Across 514 enhancers tested in mouse, we identified ‘best-in-class’ enhancer-AAVs targeting 21 atlas-defined BG populations, spanning canonical and non-canonical striatal SPN subtypes (including D1-ICj granule cells, D1-NUDAPs, and D1/D2 hybrids), GPe prototypic and arkypallidal projection neurons, STN glutamatergic neurons, anterior and posterior SNr subtypes, and dorsal- and ventral-tier midbrain dopaminergic neurons. Best-in-class enhancer-AAVs achieved >70% on-target specificity by single-cell RNA-seq, with many exceeding 90%,

and cross-species comparisons demonstrated robust preservation of specificity between mouse and macaque. Sequence-based activity modeling (CREsted) of validated enhancers identified evolutionary conservation, chromatin accessibility, and motif grammar as features predictive of *in vivo* performance. This work represents the first comprehensive cross-species enhancer-AAV toolkit for the basal ganglia, unlocking previously inaccessible cell types for precise experimental interrogation in rodents and primates, and providing the groundwork for cell type-targeted gene therapies across mammalian model systems.

Disclosures: M.E. Wirthlin: None. **S. Somasundaram:** None. **N. Taskin:** None. **N. Kempynck:** None. **M. Schmitz:** None. **E. Thomas:** None. **M. Hooper:** None. **Y. Ben-Simon:** None. **X. Opitz-Araya:** None. **J.K. Mich:** None. **A. Oster:** None. **D. Dwivedi:** None. **F.C. Collman:** None. **N. Dee:** None. **T.S. Mollenkopf:** None. **K. Smith:** None. **J. Waters:** None. **I. Ersing:** None. **N.J. Johansen:** None. **J.A. Miller:** None. **H. Zeng:** None. **E.S. Lein:** None. **Y. Kojima:** None. **G.D. Horwitz:** None. **B.P. Levi:** None. **T.L. Daigle:** None. **B. Tasic:** None. **T.E. Bakken:** None. **J.T. Ting:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.04/LL25

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

Support: NIH Grant U01MH139778

Title: Whole-brain quantitative anatomical and transcriptomic characterization of enhancer AAVs for cell type-specific targeting

Authors: D. DWIVEDI, N. LUSK, E. THOMAS, M. RUE, S. W. WAY, M. TAORMINA, A. MERRITT-JOHNSON, J. ROTH, N. DEE, J. WANG, J. ARIZA TORRES, B. THYAGARAJAN, K. RONELLENFITCH, M. REDING, S. D. HASTINGS, S. YAO, K. SMITH, Y. ISOGAI, Z. LEWIS, J. WATERS, J. T. TING, H. ZENG, *Y. BEN-SIMON, B. TASIC;
Allen Inst., Seattle, WA

Abstract: The mouse brain comprises hundreds of different cell types, with each of them contributing to different facets of animal behavior and cognition. Their transcriptomic identity has recently been defined using advanced single-cell genomics approaches. However, understanding their roles in brain function requires genetic access that would enable selective manipulation or activity monitoring of each cell type. To achieve this, we leveraged single-nucleus multiome (single-nucleus assay for transposase-accessible chromatin sequencing combined with single-nucleus RNA-sequencing) data to identify putative enhancers - cis-regulatory DNA elements that drive cell type-specific gene expression and screened them for their selective activity across regions and cell types using systemic delivery of AAVs driving

reporter expression (Ben-Simon et al., 2025). While this effort resulted in many useful reagents, both selection of enhancers, as well as their characterization, remained mostly qualitative and limited to select brain regions. Here, we present an improved pipeline for quantitative anatomical and molecular characterization enhancer AAVs. Putative enhancers were cloned into AAV backbones for expression of the nuclear trafficked fluorophore mScarlet-H2B or the attenuated iCre(R297T) recombinase. Viral vectors were packaged into blood-brain barrier-penetrant PHP.eB serotype and delivered systemically to either wild-type or H2B-EGFP-expressing Cre-reporter mice. Image sets of labeled brains were acquired using light-sheet microscopy and registered to the Allen Mouse Brain Common Coordinate Framework (CCF), enabling cell identification and signal brightness quantification. Enhancers which demonstrated a high degree of target selectivity were further evaluated using single-nucleus genomics with 10xFLEX or spatial transcriptomics with BARseq, to determine the transcriptomic identity of labeled cells. To further contextualize light-sheet data, we trained a point transformer model on Allen Brain Cell Atlas MERFISH data to infer subclass identity of CCF-registered cells and used transcriptomic data to validate its predictions. Last, we used the results from ~1400 screened mouse enhancers to train a classifier to predict top-performing enhancers across the 338 transcriptomic cell subclasses reported based on whole mouse brain profiling (Yao et al., 2023). Together, this trimodal characterization approach with model-based prediction enables comprehensive, quantitative nomination and characterization of enhancer-AAV tools at scale, accelerating the development of a comprehensive genetic toolkit for mouse brain cell types.

Disclosures: D. Dwivedi: None. **N. Lusk:** None. **E. Thomas:** None. **M. Rue:** None. **S.W. Way:** None. **M. Taormina:** None. **A. Merritt-Johnson:** None. **J. Roth:** None. **N. Dee:** None. **J. Wang:** None. **J. Ariza Torres:** None. **B. Thyagarajan:** None. **K. Ronellenfitch:** None. **M. Reding:** None. **S.D. Hastings:** None. **S. Yao:** None. **K. Smith:** None. **Y. Isogai:** None. **Z. Lewis:** None. **J. Waters:** None. **J.T. Ting:** None. **H. Zeng:** None. **Y. Ben-Simon:** None. **B. Tasic:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.05/LL26

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

Support: Allen Institute
NIH Grant R01MH134833
NIH Grant U01MH139778

Title: Enhancer-based viral tools enable genetic access to neuromodulatory cell types

Authors: O. HO-SHING, J. WANG, A. A. LAKUNINA, J. LEE, D. DWIVEDI, C. ENG, K. FANCHER, N. LUSK, X. OPITZ-ARAYA, B. THYAGARAJAN, Z. SU, E. THOMAS, S. W. WAY, K. SVOBODA, B. TASIC, S. NARAYAN, J. H. SIEGLE, Y. BEN-SIMON, J. T. TING,

***Y. ISOGAI**;
Allen Inst., Seattle, WA

Abstract: Neuromodulatory cells comprise small clusters of neurons in the mammalian brain, yet they exert outsized influence over brain-wide neural dynamics. These cells have diverse axonal projections and gene expression. Thus, isolating cell-type-specific functions typically demands complex intersectional genetics between multiple driver and reporter mouse lines.
To enable cell-type-specific access to neuromodulatory systems, we have developed enhancer-based viral tools that provide genetic access to each of four populations of neurons: norepinephrine neurons of the locus coeruleus, serotonin neurons of the dorsal raphe, dopamine neurons of the ventral tegmental area, and acetylcholine neurons of the basal forebrain. We describe a strategy to develop, screen and validate these tools using light sheet microscopy and single nucleus RNA sequencing, followed by immunohistochemistry to determine specificity and completeness of labeling. We then demonstrate their utility for delivering functional cargos such as opsins for systems neuroscience applications and present strategies for further resolving subtypes within these neuromodulatory populations using retrograde labeling.
Together, these results establish enhancer-based viral tools as a compelling route for accessing defined neuromodulatory populations, offering a streamlined alternative to transgenic intersectional approaches for functional interrogation of these high-impact circuits individually and in combination.

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Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.06/LL27

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

Support: NIMH U190MH114830
NIH U19NS123714

Title: From Transcriptomic Cell Types to Circuit Function: A Modular Platform of Driver Lines, Reporter Lines, and Enhancer AAVs.

Authors: *S. NARAYAN, T. ZHOU, B. WYNALDA, N. LUSK, A. OSTER, J. ROTH, C. HALTERMAN, K. RONELLENFITCH, S. D. HASTINGS, J. WATERS, Y. BEN-SIMON, H. ZENG, B. TASIC;
Allen Inst., Seattle, WA

Abstract: The advent of single-cell genomics has enabled systematic delineation of cell types based on gene expression profiles. As cell types are rarely defined by a single marker gene, tools that exploit intersectional expression of multiple genes are critical for achieving cell-type-specific access. We recently published a toolkit that includes driver lines and over 1,000 enhancer adeno-associated viruses (eAAV) covering most subclasses of cortical cells (Ben-Simon et al., Cell, 2025). When paired with suitable reporters, these driver lines and eAAVs provide unprecedented access to discrete cell populations. These tools are publicly accessible through the Genetic Tools Atlas (GTA; https://portal.brain-map.org/genetic-tools/genetic-tools-atlas). This toolkit is complemented by robust recombinase-responsive reporter lines in which transgene expression is driven by strong, ubiquitous promoters targeted to the Rosa26 or TIGRE genomic loci. The stability and precise transcriptional regulation at these loci accommodate large, complex, modular constructs and support intersectional targeting experiments with a high degree of precision. Reporter design determines experimental capability: fluorescent proteins enable anatomical labeling and cell quantification; genetically encoded sensors permit monitoring of neural activity; and opsins allow optogenetic manipulation of defined circuits. Here we present several examples illustrating the versatility of this modular platform, including dual-color reporters for simultaneous labeling of two distinct cell populations, dual-opsin reporters for opto-tagging experiments that assign cell-type identity during electrophysiological recordings, and all-optical reporters that combine calcium sensors with opsins for simultaneous readout and control of neural activity in genetically defined cell types. All tools are available or will be made available through JAX, and their characterization is publicly accessible through the Genetic Tools Atlas (GTA; https://portal.brain-map.org/genetic-tools/genetic-tools-atlas).

Disclosures: S. Narayan: None. **T. Zhou:** None. **B. Wynalda:** None. **N. Lusk:** None. **A. Oster:** None. **J. Roth:** None. **C. Halterman:** None. **K. Ronellenfitch:** None. **S.D. Hastings:** None. **J. Waters:** None. **Y. Ben-Simon:** None. **H. Zeng:** None. **B. Tasic:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.07/LL28

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

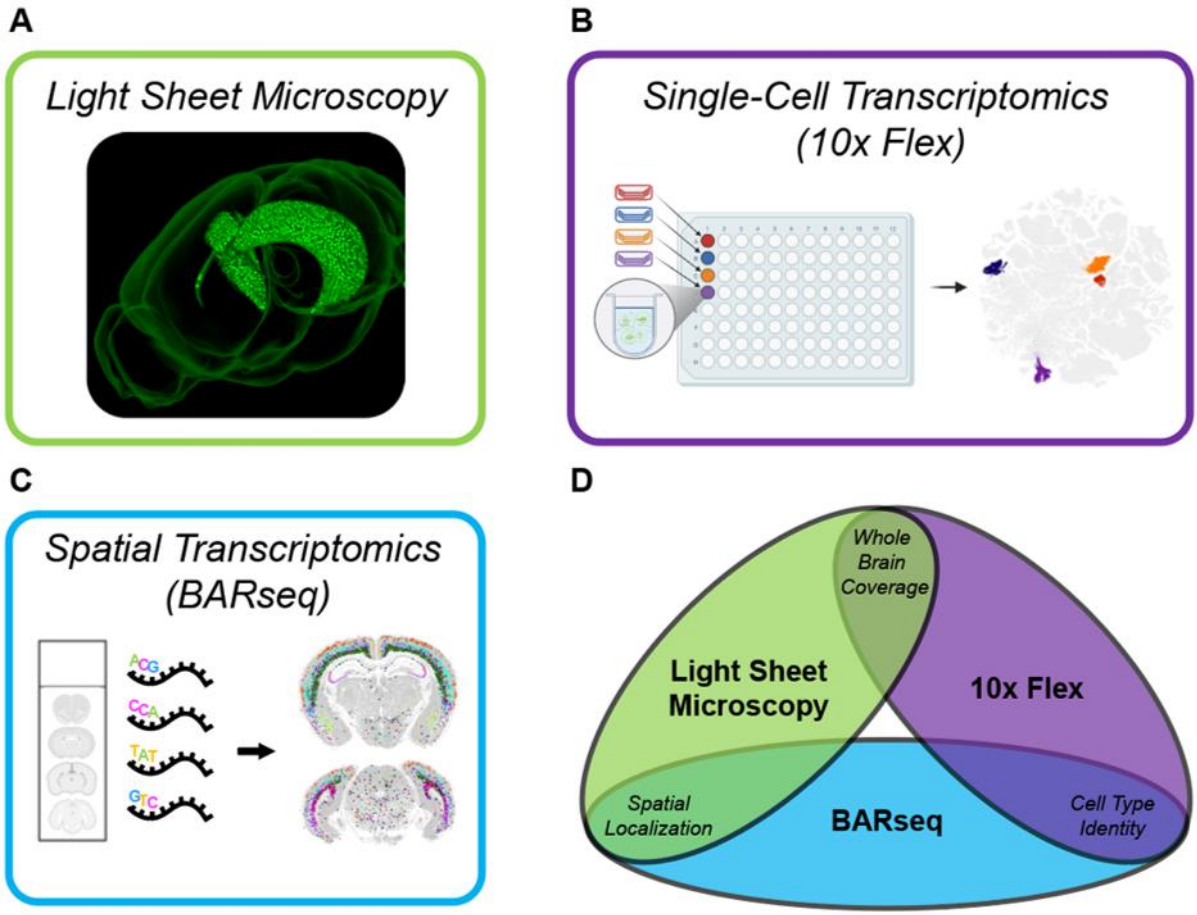
Support: NIH Grant U01MH139778

Title: Transcriptomic Characterization of Enhancer AAVs Across the Whole Mouse Brain

Authors: *E. THOMAS[1], M. RUE[2], D. DWIVEDI[1], N. LUSK[1], S. W. WAY[3], S. YAO[9], J. ARIZA TORRES[4], C. DICKSON[1], T. O'NEILL[1], S. D. HASTINGS[10], N. DEE[10], D. L. JONES[1], N. PENA[1], N. SHAPOVALOVA[1], R. D. HODGE[5], T. CARDENAS[1], A. TORKELSON[1], K. SMITH[1], P. WITTIG[1], K. RONELLENFITCH[1], M. REDING[1], J. WANG[6], Y. ISOGAI[7], B. THYAGARAJAN[1], Z. LEWIS[1], J. WATERS[1], J. T. TING[11], H. ZENG[1], Y. BEN-SIMON[1], B. TASIC[8];

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Abstract: The mouse brain is a highly complex and heterogeneous structure comprising thousands of diverse cell types. Genetic tools that can precisely and robustly label these populations are valuable assets for researchers interested in experimentally accessing or manipulating each of them. Since specific labeling of a target population is a prerequisite for a useful genetic tool, comprehensive characterization of the labeling patterns they produce prior to their distribution to the broader scientific community is crucial. To this end, we developed a pipeline for quantitative anatomical and molecular characterization of enhancer adeno-associated viruses (AAVs) and transgenic mouse lines, consisting of three independent modalities. All enhancers are initially screened via light sheet fluorescence microscopy, which provides volumetric imaging of the whole brain and a quantitative, spatially localized readout of all cells labeled by each enhancer AAV (Fig. 1A). Next, to confirm the transcriptomic identities of the labeled cells, we employ two complementary transcriptomic methods: 1) 10x Flex, which provides high cell type resolution of labeled cells at whole brain scale (Fig. 1B), and 2) BARseq, which provides transcriptomic identity of labeled cells at fine spatial resolution across select brain slices (Fig. 1C). Here, we present BARseq and 10x Flex data from a variety of different enhancer AAVs that were screened as part of this pipeline. We show that the cell type composition of each enhancer largely agrees between these two methods, as well as with light sheet data from the same viral constructs. Taken together, these three approaches allow us to comprehensively assess both spatial localization and cell type identity of labeled cells across the brain (Fig. 1D), allowing for optimal tool selection for diverse experimental designs. These characterization datasets will be released as part of the Allen Institute's Genetic Tools Atlas in early 2027 and may serve as a ground truth for models seeking to predict cell type composition based on spatial labeling patterns.



Disclosures: E. Thomas: None. **M. Rue:** None. **D. Dwivedi:** None. **N. Lusk:** None. **S.W. Way:** None. **S. Yao:** None. **J. Ariza Torres:** None. **C. Dickson:** None. **T. O'Neill:** None. **S.D. Hastings:** None. **N. Dee:** None. **D.L. Jones:** None. **N. Pena:** None. **N. Shapovalova:** None. **R.D. Hodge:** None. **T. Cardenas:** None. **A. Torkelson:** None. **K. Smith:** None. **P. Wittig:** None. **K. Ronellenfitch:** None. **M. Reding:** None. **J. Wang:** None. **Y. Isogai:** None. **B. Thyagarajan:** None. **Z. Lewis:** None. **J. Waters:** None. **J.T. Ting:** None. **H. Zeng:** None. **Y. Ben-Simon:** None. **B. Tasic:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.08/LL29

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

Title: Transcription factor binding syntax underlying selective enhancer activity across cortical glutamatergic cell types

Authors: *J. R. ROTH, A. MERRITT-JOHNSON, D. DWIVEDI, Y. BEN-SIMON;
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Abstract: Enhancers are short noncoding DNA sequences that regulate transcription and help establish the gene expression programs that define distinct cell populations. Many cell type-specific enhancers have recently been identified and used to build viral toolkits that enable selective access to cell types in the mouse brain. However, the mechanisms that drive cell type-specific enhancer activity remain poorly understood. A better understanding of these mechanisms could enable the systematic design of synthetic enhancer-based tools for more precise genetic access.
Enhancer function is mediated primarily by transcription factors (TFs), which recognize and bind specific DNA sequences. Because each TF has distinct sequence preferences, differences in TF expression across cell types may help explain cell type-specific enhancer activity. To examine this relationship, we analyzed characterization data from more than 700 putative mouse enhancer sequences identified by differential chromatin accessibility across cortical cell types and screened through systemic AAV delivery. We mapped transcription factor binding sites (TFBSs) across all sequences using the JASPAR database and evaluated differential TF expression across the different cortical cell types. Focusing on four distinct and visually discernable cortical glutamatergic populations — L2-3_IT, L5_ET, L6_IT_Car3, and L6b — we found that certain sites recognized by differentially-expressed TFs were enriched in on-target enhancers (putative activators), whereas others were depleted (putative repressors), when compared with all other functional and non-functional enhancers. We also identified a TFBS syntax defined by motif spacing and arrangement in on-target enhancers that may underlie cell type specificity. To empirically test this, we removed key putative activator motifs from enhancers targeting each population and evaluated labeling efficiency qualitatively in vivo after systemic retro-orbital injection and quantitatively ex vivo in organotypic slice cultures. These deletions revealed a hierarchy of motif importance: some sites were essential, and their removal caused complete loss of specificity, whereas others had little or no effect. Together, these results show that enhancer function depends on a critical subset of regulatory motifs arranged in a defined syntax. More broadly, this work advances our understanding of how chromatin accessibility, transcription factor binding, and gene regulation interact to produce cell type-specific expression in the mouse cortex and beyond.

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Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.09/LL30

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

Support: NIH/NIA R01AG078565
Shriners 87530-PHI-22

Title: Development of Cre-dependent FlpO-expressing mice for OPC-targeted intersectional studies

Authors: *J. COAKLEY[1], V. BUI[2], S. H. KANG[3];
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Abstract: The expression of NG2, PDGFRa, or Matrilin-4 serves as a cell-specific marker of oligodendrocyte precursor cells (OPCs), and the promoters of these genes have been used for mouse genetic engineering in OPC-focused studies. However, the sole use of each gene promoter or locus results in unintended additional sampling of other brain cell types, such as pericytes, perivascular fibroblasts, and neurons. To enhance target cell specificity while expanding the scope of OPC-targeted studies into more complex biological contexts, we generated a novel knock-in mouse line, *NG2-cRibo-Flp*, that expresses FlpO recombinase under the *Cspg4* promoter in a Cre-dependent manner. In *NG2-cRibo-Flp* mice, the transgene includes HA-tagged RPL22 sequences upstream of FlpO, separated by T2A. This setup allows immunoprecipitation of translating ribosomes for mRNA isolation. When crossed with *Olig2-Cre* or *Sox10-CreER* and with tdTomato-expressing Flp recombinase reporter mice (Ai65F), the resulting triple transgenic mice expressed tdTomato and HA-RPL22 exclusively in OPCs, without sampling other types of cells. While tdTomato-labeled OPCs differentiated into tdTomato+ mature oligodendrocytes over time, HA-tagged RPL22 expression remained in $NG2^+$ OPCs even after a long period of time. Similarly, crossing the *NG2-cRibo-Flp* mice with *Pdgfrb-CreER* resulted in tdTomato and HA expression confined to $NG2^+PDGFR\beta^+$ pericytes. We tested the *NG2-cRibo-Flp; Sox10-CreER; Ai65F* mice by exposing them to traumatic brain injury (TBI) to examine OPC lineage progression and assess OPC-specific transcriptomic changes in response to injury. We compared these results with those from *NG2-CreER; RiboTag; Ai14* mice. Our findings demonstrated that *NG2-cRibo-Flp* mice selectively sample distinct subsets of NG2-expressing cells, depending on the Cre line used. The *NG2-cRibo-Flp* mice will serve as a superior tool for more advanced analyses of cell-specific OPC fate tracing, morphological analysis, and gene expression profiling, particularly in experimental settings where reliable OPC analyses are difficult to achieve.

Disclosures: J. Coakley: None. **V. Bui:** None. **S.H. Kang:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.10/LL31

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

Title: An orthogonal TRAP enables intersectional genetic access to activated neurons in the mouse brain

Authors: *N. CHATZIRIS[1], B. JARVIE[1,3], C. LIU[3], Z. KNIGHT[1,2,3];
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Abstract: The study of neural circuits has been greatly enabled by methods for obtaining genetic access to activated neurons. However, these approaches typically tag neurons based on their response to only a single stimulus, which limits the ability to define precise subpopulations of cells. Here we describe an approach (X-TRAP) in which the activity-dependent expression of Flp recombinase is gated by branaplam, a small molecule that triggers splicing of the X-ON switch. We show that X-TRAP knock-in mice exhibit undetectable Flp recombination in the absence of drug and that branaplam treatment results in robust induction of recombination selectively in neurons that express FOS. Moreover, we show that X-TRAP is orthogonal to the widely-used TRAP system, such that these two approaches can be used in the same animal to label cells with Cre and Flp recombination in response to two different stimuli. We apply this strategy to generate intersectional maps of neuronal populations activated by GLP-1-induced satiety and nausea, revealing overlapping and distinct subpopulations across the brain that contribute to these responses. This approach for intersectional, activity-dependent genetic labeling should improve our ability to identify neural circuits underlying behavior with greater specificity.

Disclosures: N. Chatziris: None. **B. Jarvie:** None. **C. Liu:** None. **Z. Knight:** None.

Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.11/LL32

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

Title: A Tunable Dual-Control Positional Knock-in Platform for Regulated NIBP/TRAPPC9 Expression

Authors: *R. HOSSAIN[1], D. ZHANG[1], X. YUAN[1], A. BALOCH[2], D. JAIJYAN[1], J. XU[1], B. ANGELES[1], I. SISTO[1], W. HU[1];
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Abstract: NIK- and IKK2-binding protein (NIBP), also known as TRAACP9, is a multifunctional protein implicated in NF-kB signaling, intracellular trafficking, trans-Golgi network function, and neurodevelopment. Pathogenic variants in TRAPPC9 cause a monogenic autosomal recessive neurodevelopmental disorder, but the cell -type- and time-dependent functions of NIBP remain incompletely understood. Existing models allow loss-of-function analysis or Cre-mediated cell-type specificity, but few systems permit combined spatial

activation with inducible regulation of NIBP expression. To address this gap, we developed a dual-control Rosa26 positional knock-in mouse platform carrying a CAG-CuO-loxP-STOP-loxP-NIBP-smFP-2A-tdTomato cassette. This design combines Cre/CreERT2-mediated activation with cumate/CymR-mediated transcriptional regulation. The NIBP-smFP-HA tag enables sensitive detection of endogenous NIBP expression and subcellular distribution, while tdTomato provides a fluorescent report of cassette activity. We first tested Cre-dependent activation by infecting NIBP knock-in neural stem cells with Adeno-Cre, followed by differentiation and confocal imaging. We also crossed NIBP knock-in mice with Cre or CreERT2 driver mice to assess reporter activation in vivo. Qualitative imaging showed tdTomato and NIBP-smFP signal in cultured neural cells and reporter signal in brain and enteric tissues in vivo. To test the inducible regulatory arm, we delivered CymR using a lentiviral CymR-GFP vector in NIBP knock-in neural stem cells. GFP signal was consistent with CymR-GFP delivery, and co-delivery with Adeno-Cre was associated with reduced tdTomato signal relative to Cre-only controls, supporting CymR-associated repression. Cumate treatment supported tdTomato reporter activation, consistent with release of CymR-mediated repression. Together, these qualitative proof-of-concept studies support the feasibility of a dual-control NIBP/TRAPPC9 expression platform. Future quantitative studies will define induction efficiency, repression strength, and ON-OFF-ON reversibility. This system provides a foundation for studying dosage-, time-, and cell-type-dependent NIBP/TRAPPC9 function in neurodevelopment, neuroinflammation, neurodegeneration, and viral infection-related disease contexts.

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Poster

PSTR290: Genetic Techniques

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

Support: NINDS/NIA: 1R56NS138538-01
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NASA K80NSSC21K027
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Title: Harnessing DNA Damage Response for Precision Epigenome Editing: Therapeutic Implications for Neurodegenerative Disorders and Deep Space Exploration

Authors: *X. ZHANG[1], X. TIAN[2], J. LI[3], E. KNOTT[4], D. LU[6], J. CHANCELLOR[7], L. HARRISON[5], X. LU[8];
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Abstract: Genomic instability (increased frequency of mutations in a genome) is recognized as the foremost of the twelve hallmarks of aging. Neuronal genomic instability is featured in both aged individuals and those suffering from neurodegenerative disorders (NDDs) like Alzheimer's disease (AD). Mounting evidence indicates that the DNA damage response (DDR) to genomic instability is persistently activated and becomes maladaptive, which can drive cellular senescence, chronic neuroinflammation, autophagy-lysosome dysfunction. Intriguingly, host cells also fight against virus invasion via DDR pathways. DDR is thus detrimental to viral life cycles and can be considered an innate antiviral host defense mechanism. Host DDR pathway, e.g., ATM, DNA-PKCS, and the MRN complex, plays an inhibitory role in AAV genome processing, including double-strand genome conversion and genome circularization or multimerization. Based on the concept, we designed a genetic Probe with a viRal proxy for the Instability of DNA surveillance/repair in Somatic brain Mosaicism (PRISM) that harnessed the genome processing mechanism of rAAV and the instability of a hypermutable microsatellite sequence. We generated the first-ever brain map of genotoxic instability in mice exposed to Moon and Mars mission-related doses of Galactic Cosmic Radiation (GCR). In CNS, the DDR is highly dynamic and mosaic across different cell types and developmental stages. Conventional genetic approaches with constitutive knockouts/downs or overexpression risk disrupting normal cellular function and do not reflect the cell-type-specific, context-dependent nature of DDR signaling. To untangle the complexity, a seek-and-rescue genetic strategy was developed for precise genetic perturbation selectively in the cells burdened with persistent and overactive DDR to genomic instability. A critical advantage of this strategy is that epigenetic modulation is transient, as the effector expression is not constitutive and dependent on the existence of overactive and persistent DDR to genotoxic stress. We demonstrated the robust efficacy of such an approach in rescuing neuropathology and behavioral deficits in synuclinopathy and AD animal models. Our approach will advance technological and conceptual innovation to improve repeated measures across longer epochs of the lifespan in the aging brain and AD/ADRD. Single-cell selective and transient epigenetic modulation of maladaptive DDR unravels the causal pathogenic role of genomic instability and holds potential for "single-cell precision medicine " as a disease-modifying strategy to a wide range of CNS disorders associated with genomic instability.

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Poster

PSTR290: Genetic Techniques

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR290.13/LL34

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

Title: Whole-Gene Humanization in Mouse Cells via Twin Prime Editing and eeBxb1-Mediated Cassette Exchange to Generate Humanized Mouse Models of Neurological Disease

Authors: *T. F. SALTER-CID[1,2], A. GUGLIELMI[2], C. CAPUTO[3,2], H. O'GEEN[2], D. SEGAL[2,4,5];
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Abstract: Introduction: Mouse models are foundational to neuroscience, yet on average only ~80% of the mouse exome is identical to the human sequence. Murine orthologs therefore do not always reproduce the function of human disease variants, limiting faithful modeling of human neurological disorders. Replacing an entire endogenous mouse gene with its full-length human counterpart ("whole-gene humanization") could resolve this, but current approaches—Cas9-driven homology-directed repair, recombinase-mediated cassette exchange (RMCE), and PiggyBac transposition—suffer from low efficiency, high insertion-deletion rates, and off-target effects. These limitations are most severe for large loci (>15 kb) and have restricted humanization to a handful of genes.
Methods: We developed a double-strand-break (DSB)-free platform that combines multiplexed twin prime editing and eeBxb1-mediated RMCE in a single step. Twin prime editing installs two ~50-bp Bxb1 attachment sites flanking an endogenous mouse gene without generating DSBs, enabling multiplexed insertion with minimal indels. Co-delivered in the same reaction, the serine integrase eeBxb1 then swaps the bracketed mouse locus for a full-length human transgene, so both landing-pad installation and gene replacement occur in one step.
Results: As proof of concept at the Ccr5 locus in Neuro-2a (N2a) neuroblastoma cells, we achieved >85% single-site insertion and ~55% multiplexed installation of both attachment sites in cis (on the same allele), and ~14% single-step replacement of the mouse locus with the human ortholog at a kilobase-scale (~1.2-1.4 kb) gene, without antibiotic selection; antibiotic-based enrichment to further increase this rate is ongoing. We are now extending the platform to larger, disease-relevant neuronal genes spanning ~5-14 kb: Scg2 (secretogranin II, a neurosecretory granule protein), Kcna2 (the Kv1.2 voltage-gated potassium channel), and Irx6 (an Iroquois-class homeobox transcription factor). Using an optimized prime editor, we already obtain 63-92% landing-pad insertion across these loci.
Conclusions: These data establish a scalable, DSB-free route to whole-gene humanization with high efficiency and low off-target burden. Extending the approach to mouse embryonic stem cells will enable fully humanized mouse models for studying neurological disease.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.01/LL35

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

Support: NSF DBI 2015317
NSF FRR IIS-2138873

Title: A spiking sequence generator for polar trajectories on neuromorphic hardware

Authors: *W. R. P. NOURSE[1], R. D. QUINN[2];
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Abstract: Neuromorphic controllers for size, weight, and power-constrained systems require neural architectures that are both energy-efficient and interpretable at the level of system dynamics. However, existing approaches either rely on end-to-end trained spiking networks with limited interpretability, or on converted classical controllers that fail to fully exploit neuromorphic dynamics. We present a spiking neural network (SNN) architecture for generating polar trajectories, using a winner-take-all (WTA) architecture with accessory populations that induce controlled transitions in neural activity. We demonstrate tuning rules for these population dynamics, and utilize a form of shunting inhibition to enable independent control of direction, speed, and radius of the resulting polar trajectories. We implement the network on the SpiNNaker2 neuromorphic processor, and demonstrate a two to three orders of magnitude reduction in wall-clock step time and three to four orders of magnitude reduction in energy expenditure when compared to conventional computing platforms.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.02/LL36

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

Title: Structure-based computational screening of environmental neurotoxicants at the picrotoxin site of the $GABA_a$ receptor: recovery of known organochlorine channel blockers and the limits of docking-score interpretation

Authors: *B. O. OYETAYO[1,2], A. O. ADERIBIGBE[3];
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Abstract: Environmental neurotoxicants are widespread, yet their direct interaction with the $GABA_a$ receptor, a central mediator of inhibitory neurotransmission, remains incompletely characterized. We performed a structure-based computational screen of 20 environmental neurotoxicants against the picrotoxin binding site of the human $GABA_a$ ρ1 receptor (PDB

8OQA) using AutoDock Vina, with the protocol validated by redocking the co-crystallized antagonist picrotoxin to a heavy-atom RMSD of 1.44 Å. The cyclodiene organochlorines aldrin (−8.9 kcal/mol), dieldrin (−8.9 kcal/mol), heptachlor and chlordane ranked among the strongest binders alongside picrotoxin itself (−8.7 kcal/mol), in agreement with their established pharmacology as GABA-gated chloride channel blockers. Organophosphates bound comparatively weakly (−5.3 to −5.7 kcal/mol), consistent with their primary action through acetylcholinesterase. Three-dimensional pharmacophores overlap with picrotoxin correlated only weakly with predicted affinity ($R = -0.49$, $R^2 = 0.24$, $p = 0.024$), and exploratory cross-validated modelling identified molecular size and ring count, rather than specific pharmacophore features, as the dominant correlates of docking score. Non-binding controls were not cleanly separated from the toxicants, indicating that absolute docking scores are confounded by molecular size and lipophilicity. Benchmarked against receptor-matched experimental potencies measured on the same human ρ1 receptor, the predicted scores were inversely related to measured potency (Pearson $r = -0.79$, $n = 5$): the most potent compound at ρ1 (lindane) was predicted to bind weakly, whereas picrotoxin and fipronil, which are weak at ρ1, scored among the strongest, and even the co-crystallized reference compound was misranked. We therefore interpret these results through relative ranking and concordance with known biology rather than as quantitative affinities. The screen recovers the recognized organochlorine $GABA_a$ antagonists and provides structure-based hypotheses to prioritize compounds for experimental validation.

Disclosures: B.O. Oyetayo: None. **A.O. Aderibigbe:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

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Program #/Poster #: PSTR291.03/LL37

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

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New Cornerstone Investigator and a Shanghai Academy of Natural Sciences (SANS) Senior Investigator

Title: Morphology-to-function modeling at scale enables a large-scale dataset of human single-neuron models

Authors: *Y. WEI[1], N. GE[3], Y. LIU[2], H. PENG[2];
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Abstract: Biophysically detailed neuron models are essential for linking cellular structure to neural dynamics, yet their large-scale construction remains limited by labor-intensive electrophysiological measurements. Here we show that neuronal morphology defines a structural prior that constrains electrophysiological dynamics. Building on this principle, we develop a scalable framework that infers ion channel parameters directly from morphological features and integrates automated simulation and validation. Applying this framework to more than 10,000 reconstructed human neurons, we generated a large-scale dataset of biophysically detailed human single-neuron models. The predicted models recapitulate key firing dynamics and population-level statistics observed in experimentally fitted neurons. Mechanistically, neuronal excitability is governed by low-dimensional interactions among ion channel parameters constrained by morphology. By bridging structure and function at scale, our work establishes a data-driven foundation for modeling neuronal dynamics and represents a critical step toward constructing biologically grounded virtual brains.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

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Program #/Poster #: PSTR291.04/LL38

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

Support: HHMI
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Title: Connectome, transcriptome and task constrained models of the entire fly optic lobe

Authors: *Z. STEFANIDI[1,2], L. ULMER[1,2], B. KIM[1,2], I. OMOLAYO[1,2], M. MCGILL[3], J. LAPPALAINEN[1,2], N. C. KLAPOETKE[3], Y. KURMANGALIYEV[4], A. NERN[3], S. TURAGA[3], J. H. MACKE[5,1,2];
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Abstract: In the fruit fly, over half of the brain is dedicated to visual processing. Recent connectome datasets cover the entire optic lobe at synaptic resolution, providing a structural basis for modeling neural computations across the visual system *(Nern et al. 2025, Dorkenwald et al. 2024)*. Connectome-constrained deep mechanistic network (DMN) models, task-optimized for motion detection, have previously predicted motion tuning properties *(Lappalainen et al. 2024)*, but were limited to convolutional approximations of a subset of the motion pathway. Our

goal here is to build connectome-constrained DMN models of the whole optic lobe, to generate detailed, cell-by-cell hypotheses of circuit mechanisms throughout the visual system. We first constructed a connectome graph of the entire optic lobe from the *Nern et al.* connectome. Since the photoreceptors and lamina in this dataset are truncated, we imputed *~4,000* neurons and *~1.2M* synaptic connections across *19* cell types, based on intact components and light microscopy data *(Tuthill et al. 2014)*. We then built a DMN model using this connectome graph, applying morphology-driven compartmentalization where point-neuron approximations fail *(Seung 2025)*, and incorporated conductance-based synapse dynamics to capture nonlinear synaptic computation *(Groschner et al. 2022)*. After training the DMN on a motion detection task, it robustly predicted known tuning properties. Notably, our model showed improved predictions compared to previous work, e.g. for OFF-motion direction selectivity in T5 cells, while reducing variability across an ensemble of trained models. Finally, scaling connectome-constrained models to the full optic lobe poses a major challenge due to many unconstrained parameters. To address this, we leveraged transcriptome data by sharing network parameters based on transcriptomic similarity, making it possible to propagate parameter values to pathways unconstrained by the motion detection task. We further constrained parameters by integrating neural activity recordings from *50+* cell types across multiple modalities. Our results demonstrate an approach for scaling connectome-constrained models with a one-to-one mapping between biological and artificial neurons.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.05/LL39

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

Support: NRF Grant RS-2025-00557395
NRF Grant RS-2025-17492968

Title: Computational modeling of microtubule-mediated focused ultrasound modulation of neuronal excitability using Allen biophysical neuron models

Authors: *D.-H. KWON, H. KIM;
Dept. of Electrical Engin., POSTECH, Pohang, Gyeongbuk, Korea, Republic of

Abstract: Focused ultrasound (FUS) may alter neural activity beyond direct ion-channel gating. Prior theoretical modeling suggests that microtubules (MTs) may exhibit mechanical resonance in the MHz range. We therefore investigated a cell-level model in which FUS near the predicted MT-resonant frequency generates local strain gradients in the cytoskeleton. These gradients may

induce MT-mediated flexoelectric polarization, shifting the membrane operating point and altering spike probability. Our goal was to build an in silico bridge from MT electromechanics to type-specific firing using Allen biophysical neuron models. We first rebuilt the Allen model workflow as the baseline platform for FUS simulations - not as an independent replication but as a necessary control confirming that the same code could preserve known cell-type firing patterns before any FUS term was added. We reproduced morphology-linked voltage traces, action potential waveforms, model-experiment spike-count comparisons, and feature-error maps across inhibitory (Pvalb, Sst, Htr3a) and excitatory (Nr5a1, Rbp4, Ntsr1) cell classes spanning cortical layers 2-6. Thus, the Allen models provided a validated set of active neurons whose intrinsic conductance parameters could remain fixed during FUS testing. We then added a reduced FUS-equivalent input in NEURON. This input represents the predicted downstream effect of MT-flexoelectric coupling, not direct changes in sodium, potassium, or leak conductance. In the first proof-of-concept stage, we applied the input to a passive single-compartment neuron. The FUS-equivalent envelope produced clear membrane depolarization during the stimulation window and gradual recovery after offset. We also used the passive run as a scale check: the passive membrane showed clear depolarization (~16 mV shift) during the stimulation window, confirming that the proposed drive can engage the membrane before spike-generating currents are recruited. This result established the minimum effective input magnitude for subsequent active-model sweeps. It also reduced the risk of overfitting later model steps. The next stage will place the same coupling term into active Allen neurons. Rather than forcing all cell types to show the same response, we will fit only FUS-coupling variables: input amplitude, time course, and nonlocal spread within the cell. Main outputs will include resting membrane shift, rheobase, spike probability, spontaneous firing threshold, and type-specific sensitivity. This framework provides a testable model for asking whether MT-mediated ultrasound can differentially recruit cortical neuron types.

Disclosures: D. Kwon: None. **H. Kim:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.06/LL40

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

Support: NIH Grant R01NS011613

Title: Machine learning reduction of biophysical models for multi-scale stimulation analysis

Authors: J. LI[1], *R. A. MCDOUGAL[2];
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Abstract: Biophysical neuron models are widely used to study neuronal dynamics across temporal and spatial scales. These span from the four states of the classic Hodgkin-Huxley

model with its voltage-gated Na+ and K+ ion channels to modern models with thousands of compartments and many types of ion channels. We can never fully capture the state of the cell and must instead make inferences based on limited experimental observations or simulations. Previous evidence suggests that neuronal spiking behavior is primarily constrained by recent causal stimulus events, raising the possibility that neuronal dynamics may be represented using a reduced event-driven state. Consequently, we developed a machine-learning reduction framework that learns neuronal state representations from recent synaptic event histories. Recent excitatory and inhibitory events were encoded by recurrent neural networks (LSTM/GRU) into a reduced neuronal state representation. A multilayer perceptron was used to predict spike occurrence and next-spike time (NST). The framework was further evaluated in a 40,000 ms simulation with 200 Hz excitatory and 67 Hz inhibitory inputs to assess long-term temporal stability. Trained on a dataset of over one million stimulation trials and tested on 38k trials, the framework achieved a next-spike timing (NST) mean absolute error of 0.07 ms, approaching the intrinsic temporal resolution of the NEURON simulation environment, while maintaining an F1 score and AUC > 0.99 for a Hodgkin-Huxley model. Under sustained neuronal activity over a 40,000 ms simulation window containing 947 output spikes, the framework predicted 929 spikes (51 missed, 33 false-positives). In ongoing work, we are extending this to more complicated cell models and refining our training approach. Together, these findings demonstrate the feasibility of using machine-learned latent neuronal state representations as reduced models of biophysical neurons, offering the potential for accelerated simulations. Furthermore, because many neuronal variables are difficult to observe experimentally, this framework offers an alternative approach for inferring neuronal state from synaptic activity. Such reduced representations may facilitate future studies of morphologically detailed neurons, neuronal populations, and circuit-level dynamics.

Disclosures: J. Li: A. Employment/Salary (full or part-time):; Yale University. **R.A. McDougal:** A. Employment/Salary (full or part-time):; Yale University.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.07/LL41

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

Support: National Science Foundation Graduate Research Fellowship Grant DGE 2241144.
ARO MURI (Multidisciplinary University Research Initiatives) W911NF-22-1-0223
HFSP (Human Frontier Science Program) RGP0019/2018
Rackham Merit Fellowship of the University of Michigan
NSF DMS (National Science Foundation Division of Mathematical Sciences) 2052499

Title: Consequences of glymphatic-associated extracellular space expansion for ionic homeostasis and neuronal excitability across sleep-wake states

Authors: *N. C. MACLACHLAN, D. B. FORGER;
Mathematics, Univ. of Michigan, Ann Arbor, MI

Abstract: Study of the glymphatic system has revealed that the extracellular space (ECS) volume fraction expands from approximately 14% to 23% from wake to NREM sleep (Xie et al., 2013). The expansion of the ECS may not only enhance the transport of waste, but fundamentally shift neuronal excitability by modulating how ionic fluxes translate into extracellular concentration changes. To investigate this, we modify the single-cell Hodgkin-Huxley model of Cressman et al. (2009), which includes dynamic K+ and Na+, by replacing the fixed ECS volume fraction with an arousal-state-dependent parameter set to experimentally measured values for wake and NREM. We use inputs designed to mimic the recurrent excitation a neuron receives during cortical up/down states. Wake-level ECS produces runaway K+ accumulation that abolishes the down state, while NREM-level ECS yields bounded regular up/down cycling under identical input. The mechanism is geometric: a larger ECS volume attenuates the concentration change produced by a given ionic flux, preventing the positive feedback between K+ accumulation and excitability that would otherwise destabilize the down state. These results position ECS volume fraction as a permissive parameter for slow-wave activity: it does not generate the rhythm, but determines whether recurrent excitation produces stable up/down cycling or runaway K+ accumulation. Thus we propose that glymphatic-associated expansion of ECS may be a contributing factor to the characteristic slow-wave electrical activity during NREM. Building on these single-cell observations, we extend this framework to a large-scale cortical network (N>200,000 Hodgkin-Huxley neurons) grounded in Allen Brain Atlas spatial transcriptomics and viral projection-based connectivity to examine whether and how ECS volume fraction shapes the emergence, stability, and spatial organization of slow oscillations at the population level.

Disclosures: N.C. MacLachlan: None. **D.B. Forger:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.08/LL42

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

Support: Brain/MINDS 2.0, Japan Agency for Medical Research and Development (AMED)

Title: Neuro-Workflow: From Machine-Interpretable Brain Models to Collective Human-Agent Intelligence for Scientific Discovery

Authors: *C. GUTIERREZ[1], H. SKIBBE[2], K. MITROFANOV[1], Y. OKUMURA[2], Y. YAMANE[1], K. DOYA[1];
[1]Okinawa Inst. of Sci. and Technol. Grad. Univ., Okinawa, Japan; [2]RIKEN Ctr. for Brain Sci., Wako, Japan

Abstract: Advances in AI is revolutionizing the process of science and software development. However, computational brain modeling remains largely inaccessible to AI reasoning due to heterogeneous, tool-specific implementations of model building, simulation and analysis that lacks machine-interpretable structure. Neuro-Workflow (https://github.com/oist/neuro-workflow) addresses this by organizing modeling and analysis as a graph of machine-interpretable nodes, each defined by a schema specifying its role, inputs, outputs, and parameters. Importantly, not only new brain models can be built as structured workflows, but existing open-source neuroscience models and pipelines can be converted into AI-readable nodes, progressively expanding an interoperable library of brain modeling resources. To exploit this structure, we assign specialized agents to distinct layers: a model agent understands model components and architecture; a data agent searches experimental datasets and extract model parameters; a simulation agent interprets neural dynamics in reference to brain region identities. As preliminary demonstrations, we implemented a macaque basal ganglia spiking network using NEST and a marmoset resting-state whole-brain simulation using The Virtual Brain (TVB), both organized as Neuro-Workflow graphs in which a specialized agent navigates components, inspect parameters, and assist in workflow-generation for simulation. Because each agent operates on well-defined, machine-readable units, agent-to-agent communication becomes tractable, enabling coordinated multi-agent behavior. This bottom-up approach, grounding AI understanding in the atomic components of brain modeling, creates a scalable pathway toward collective human-agent collaboration on long-horizon scientific tasks, including systematic hypothesis testing, biomarker detection, and identification of candidate therapeutic targets. Neuro-Workflow thus positions structured brain modeling infrastructure as the foundation for AI-accelerated neuroscientific discovery, where human expertise as the Neuro-Workflow backbone is encoded in reusable components and agents and humans jointly build, test, and extend computational models of the brain.

Disclosures: C. Gutierrez: None. **H. skibbe:** None. **K. Mitrofanov:** None. **Y. Okumura:** None. **Y. Yamane:** None. **K. Doya:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.09/LL43

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

Support: EBRAINS 2.0 Project
Virtual Brain Twin Project

Italian PRIN 2022 NEAT-MOVE
MNESYS Project

Title: A biologically-grounded cerebellar spiking network model with realistic synaptic transmission captures complex circuit dynamics

Authors: *M. DE GRAZIA[1], D. BENOZZO[1], F. MARCHETTI[1], E. MENGOZZI[2], E. D'ANGELO[3,5], C. CASELLATO[4,5], D. RODARIE[1];
[1]Dept. of Brain and Behavioural Sci., Univ. of Pavia, Pavia, Italy; [2]Univ. of Pavia, Milan, Italy; [3]Brain and Behavioral Sci., [4]Dept. of Brain and Behavioral Sci., Univ. of Pavia, Pavia, Italy; [5]Digital Neurosci. Center, IRCCS Mondino Fndn., Pavia, Italy

Abstract: Cerebellar network dynamics rely on the interplay between synaptic mechanisms and intrinsic neuronal excitability, shaping cerebellar processing in both physiological and pathological states. Although detailed computational models have reproduced individual neuron and microcircuit dynamics, their computational cost limits large-scale applications.Here, we present a computationally efficient Spiking Neural Network (SNN) framework derived from a detailed cerebellar microcircuit model (De Schepper et al., 2022). It retains the main electrophysiological, synaptic, and connectivity features of the original model while enabling long-duration simulations and integration into robotic systems.The cerebellar microcircuit scaffold was generated using the Brain Scaffold Builder tool. The SNN was calibrated through cell-specific point-neuron optimization based on multicompartmental reference models, synaptic kernel fitting for AMPA, NMDA, and GABA receptors, incorporation of short-term plasticity, and tuning of synaptic weights to match reference network dynamics.We first tested whether the model reproduced physiological cerebellar network dynamics by comparing simulated spiking activity with the reference model and experimental data in healthy mice. In particular, Purkinje cells, the main output neurons of the cerebellar cortex, displayed activation patterns and firing-rate ranges consistent with previous studies.We also employed Local Field Potential (LFP) proxies (Mazzoni et al., 2015) to estimate LFP responses from single-compartment models, where extracellular potentials cannot be directly computed.These proxies captured key features of the granular-layer response to mossy fiber stimulation, as shown by comparison with acute cerebellar slice recordings (Gagliano et al., 2022), and reflected short-term plasticity modulation during repetitive inputs.To assess the suitability of the framework for pathological hypothesis testing, we performed receptor-specific blockade simulations. GABAergic blockade induced network overactivation and loss of temporal precision, indicating that inhibition constrains excitability and preserves response timing. In contrast, NMDA receptor blockade reduced network activation and strongly attenuated slow components of the LFP response, supporting the role of NMDA-mediated transmission in sustaining prolonged granular layer dynamics.This bottom-up framework provides a flexible tool to explore cerebellar pathological alterations, incorporate long-term plasticity mechanisms, and enable integration into real-time closed-loop simulations.

Disclosures: M. De Grazia: None. **D. Benozzo:** None. **F. Marchetti:** None. **E. Mengozzi:** None. **E. D'Angelo:** None. **C. Casellato:** None. **D. Rodarie:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

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

Support: European Union (ERC, DeepCoMechTome, 101089288)
Germany's Excellence Strategy MLCoE – EXC number 2064/1 PN 390727645)
German Research Foundation (DFG (SPP 2041)
German Federal Ministry of Education and Research (BMBF; Tübingen AI Center, FKZ: 01IS18039A)

Title: Multi-task training of connectome-constrained models of the full fly optic lobe

Authors: *I. OMOLAYO[1,2,3], Z. STEFANIDI[2,3], L. ULMER[2,3], B. KIM[2,3], M. MCGILL[4], J. LAPPALAINEN[2,3], A. NERN[4], S. TURAGA[4], J. H. MACKE[2,3,5];
[1]Eberhard Karls Univ. of Tübingen, Tubingen, Germany; [2]Machine Learning in Science, Excellence Cluster Machine Learning, Univ. of Tübingen, Tübingen, Germany; [3]Tübingen AI Center, Univ. of Tübingen, Tübingen, Germany; [4]HHMI Janelia Res. Campus, Ashburn, VA; [5]ELLIS Inst. Tübingen, Tübingen, Germany

Abstract: Recent connectome datasets cover the entire fruit fly optic lobe at synaptic resolution (Nern et al., 2025). This has led to the development of connectome-constrained deep mechanistic networks (DMNs), models with a one-to-one mapping between biological and artificial neurons across the full visual system. Such models could generate cell-by-cell hypotheses about circuit mechanisms throughout the optic lobe, but only if their parameters can be meaningfully constrained. Previous DMN models, task-optimized for motion detection, recovered known tuning properties in the motion pathway (Lappalainen et al., 2024). However, motion detection is only one of several tasks achieved by the visual system. Thus, when scaling these models to the full optic lobe, motion detection alone does not provide sufficient constraints for the vast majority of cell types, including those relevant for survival behaviours like courtship and escape. To address this limitation, we developed a multi-task training framework for full optic-lobe DMNs. We constructed a pipeline of synthetic visual datasets tailored to ethologically relevant fly behaviours, including optic flow, looming object detection, moving-object tracking, and self-motion estimation. Each task is paired with a task-specific decoder reading from visual projection neurons, while the underlying connectome-constrained network is shared across tasks. We trained ensembles of whole optic-lobe networks on individual tasks and on joint combinations, and evaluated both task performance and the consistency of recovered single-cell tuning across ensembles.
Joint multi-task training produced more consistent solutions across ensemble members than networks trained on any single task, while matching the per-task performance of single-task baselines. Improvements in ensemble consistency extended beyond the motion pathway, into visual projection neurons and downstream cell types whose responses were not directly supervised. This approach shows that optimizing on multiple biologically relevant tasks jointly as a scalable strategy in the broader effort to build identifiable models of the full fly visual system.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

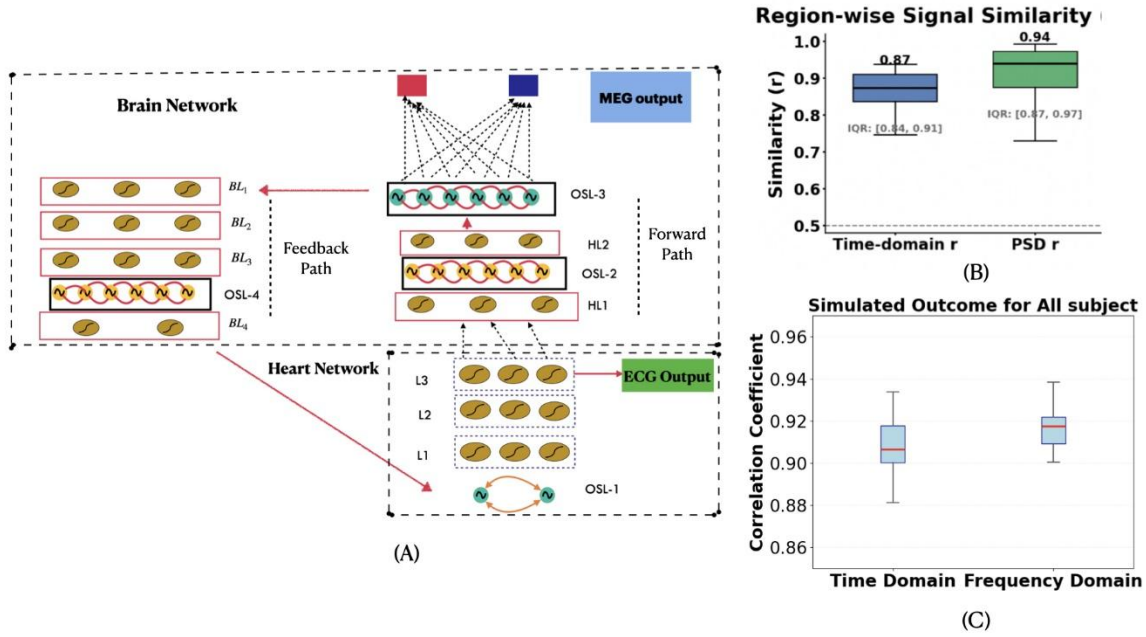
Program #/Poster #: PSTR291.11/LL45

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

Title: Modelling Simultaneous Cardiac and Brain Dynamics with Closed Loop Multimodal Oscillator System

Authors: *A. BANDYOPADHYAY[1], S. VADLAMUDI[1], D. ROY[2], S. V. CHAKRAVARTHY[3];
[1]Indian Inst. of Technol. Madras, Chennai, India; [2]Cognitive Brain Dynamics and connectivity lab, Indian Inst. of Technol., Manesar, India; [3]Dept. of Biotech., IIT Madras, Chennai, India

Abstract: To understand how the brain processes cardiac dynamics, we present a mechanistic model that describes bidirectional interactions between brain and heart dynamics by simultaneously reconstructing brain dynamics in terms of Magnetoencephalography (MEG) signals and cardiac dynamics in terms of Electroencephalogram (ECG) signals. The model has two components (Fig. A): i) the Heart Network (HN), consisting of a layer (OSL1) of coupled limit cycle oscillators (frequency range 1-1.2 Hz) and 3 layers of sigmoidal units (L1, L2 and L3 Layer) for capturing ECG signals; and (ii) the Brain Network (BN), consisting of three parts- A) the afferent autonomic inputs from the heart represented by 2 sigmoidal layers (HL1 and HL2) and a oscillator layer (OSL2, frequency range: 6-10 Hz); B) a whole brain model with a reservoir of oscillators (OSL3, frequency range 0.5-40 Hz), that reconstructs the MEG data with cardiac artefacts embedded in it. C) autonomic efferents to the heart consisting of four sigmoidal layers (BL1, BL2, BL3, BL4) and a low-frequency oscillator layer (OSL4, frequency range 6-10 Hz). The model is trained using simultaneously recorded ECG and MEG data (CAMCAN dataset) from 20 subjects. There are 4 training stages: (1) the Heart network in isolation is trained on ECG data; 2) the Brain Network is trained in isolation on MEG data from which cardiac artefacts removed; (3) the output of the trained ECG decoder (L3) is presented as input to the autonomic afferents and the Brain Network to capture MEG data with cardiac features embedded in it; (4), the brain-heart loop is closed by presenting the output of the Brain Network (OSL3) to the Heart Network and retrain the heart network. The model is trained on 10-s segments and tested on 5-s segments on MEG and ECG signals. The model output is accurate in both the time domain (average correlation coefficient: 0.92) and the frequency domain (average log-psd correlation: 0.93) (Fig. 1B for individual and Fig 1C for all subjects). The model provides a framework for studying brain-heart coupling and for potential future studies on vagus nerve stimulation.



Disclosures: A. Bandyopadhyay: None. **S. vadlamudi:** None. **D. Roy:** None. **S.V. Chakravarthy:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.12/LL46

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

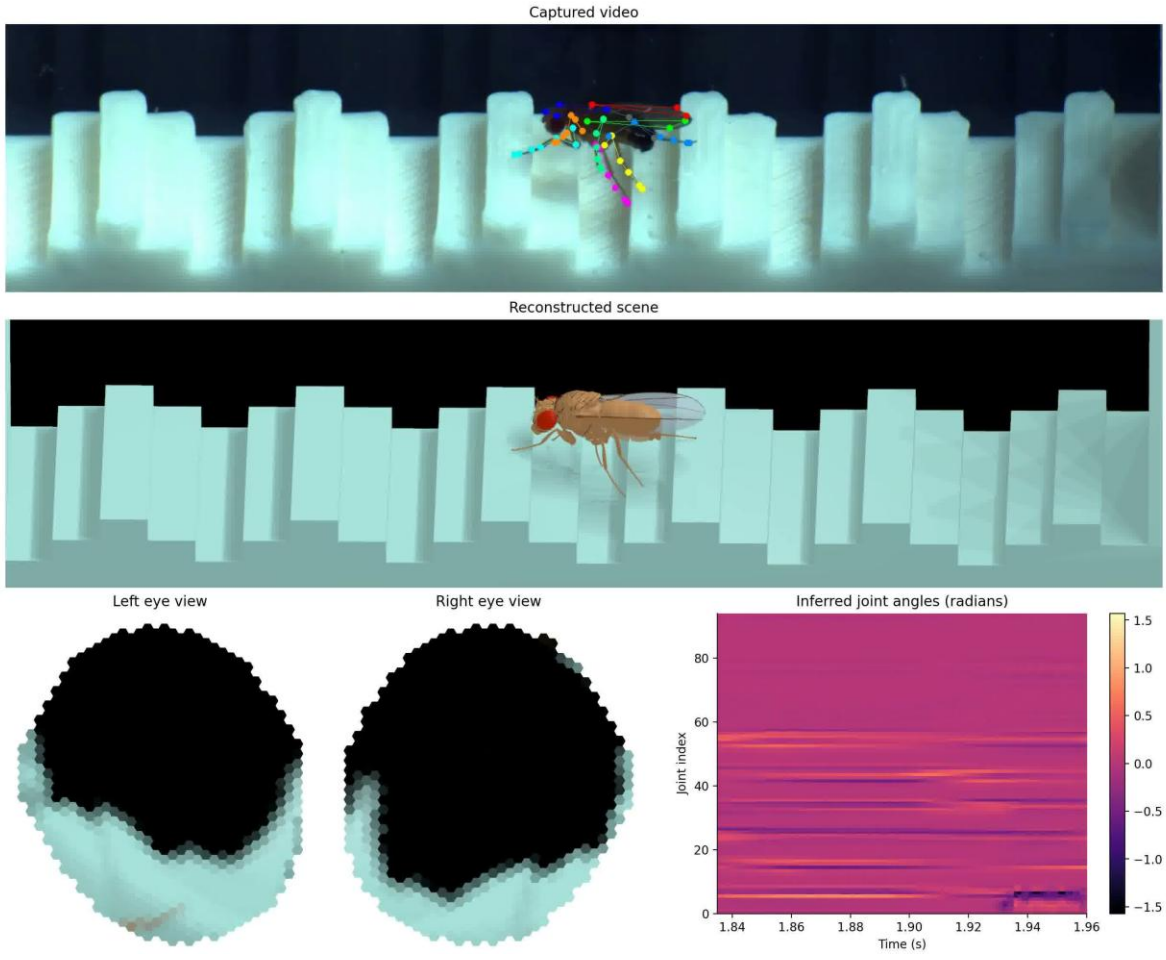
Support: Howard Hughes Medical Institute
European Research Council

Title: Body-wide physics simulation of Drosophila muscle actuation and sensory transduction

Authors: *M. MCGILL[1], G.-J. BOTH[1], J. ELLIS-JOYCE[1], M. EBERLE[2], I. SIWANOWICZ[1], R. VAXENBURG[1], S. TATA RAMALINGASETTY[1], A. BATES[3], J. I. ISPIZUA[4], E. ABE[4], J. YAN[1], R. OTHAYOTH[1], A. W. AZEVEDO[4], J. TUTHILL[4], B. W. BRUNTON[4], J. H. MACKE[5], W. KORFF[1], R. JOHNSON[1], S. TURAGA[1];
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Abstract: We extend the Drosophila whole-body physics model presented in Vaxenburg et al. (2025) with body-wide mechanosensation, proprioception, vision, and musculature, and use this

model to estimate the nervous system's inputs and outputs during behavioral experiments. We used confocal imaging of an adult female fly to determine the locations of sensory bristles, hair plates, and campaniform sensilla, as well as muscle origin and insertion points. For each sensor, we define experimentally derived functional models to predict the input current to mapped sensory neurons. The projective geometry of our eye model was derived from the positions and orientations of individual ommatidia localized in a μCT scan of a second fly's head, which we aligned to the other elements of our body model. We use a stiff-tendon Hill-type muscle model, and model the cuticle as a spring exerting a restoring force on each joint toward an equilibrium joint angle. Since direct measurements of the parameters governing the dynamics of these model components are not available, we use iterative optimization to identify regions of the parameter space consistent with a wide range of behavioral data, including walking, courtship, and grooming. After discovering plausible parameter sets, we use inverse kinematics and inverse dynamics to estimate flies' sensory inputs and motor outputs from video captured during behavioral experiments. We construct a library of these sensorimotor reconstructions from a variety of experimental setups as a resource to inform fine-grained models of fly behavior and neural function.



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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.13/LL47

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

Support: NIH Grant R01NS125376

Title: Next-Generation Axon Model for Studying Kilohertz-Frequency Nerve Conduction Block

Authors: *T. J. SMITH, N. A. PELOT, W. M. GRILL;
Biomed. Engin., Duke Univ., Durham, NC

Abstract: For over two decades, the McIntyre-Richardson-Grill (MRG) model has served as the gold standard for simulating large myelinated peripheral nerve fibers. Despite its widespread use, the MRG model exhibits important limitations in regimes relevant to kilohertz frequency (KHF) conduction block, including inaccurate predictions of onset activity. Here, we present an update to the large myelinated axon model that attempts to address this shortcoming through integration of contemporary ultrastructural data, revised ion channel representations, and parameter optimization. We first incorporated an expanded set of ultrastructural measurements from literature on the morphology of large myelinated peripheral axons. Among these updates, the most pronounced change was an ~80% reduction in juxtaparanodal length relative to the MRG model. We next incorporated specific ion channel isoforms consistent with current experimental evidence from mammalian axons. Generalized sodium (fast and persistent) and potassium (slow) conductances in the nodes of Ranvier of the MRG model were replaced with Nav1.6, Kv7.2/7.3, two-pore-domain potassium (K2P), and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, while Kv1.1/1.2 channels were incorporated into the juxtaparanode. Finally, biophysical parameters of the new model were optimized to reproduce experimental recordings. In a 10 μm-diameter fiber, the updated model preserved baseline conduction properties, with conduction velocity and activation thresholds differing by less than 3% and 1%, respectively, from the MRG model. We also simulated firing fidelity, by stimulating at 100 to 50,000 pulses per second and quantifying the percent of pulses that yielded an action potential; action potential success rate declined progressively with increasing stimulation frequency, falling below 50% at ~1500 pulses/s. Under KHF stimulation, application of a 10 kHz extracellular signal produced high-frequency onset-like activity for hundreds of milliseconds compared to <10 ms in the MRG model, representing progress towards a more physiologically realistic onset response. Although these model updates align with literature-derived excitation properties, additional refinements are

still required to capture accurately KHF nerve conduction block phenomena. Overall, this work demonstrates the potential of a more physiologically grounded and extensible axon model for studying KHF conduction block and lays the foundation for future developments toward selective neuromodulation strategies.

Disclosures: T.J. Smith: None. **N.A. Pelot:** None. **W.M. Grill:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

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Program #/Poster #: PSTR291.14/LL48

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

Support: AFOSR YIP Grant FA9550-23-1-0173
DOE Office of Science ASCR via the ECRP Grant DE-SC0025567

Title: Exploration of Tuning Neuron Models for Biological Plausibility

Authors: *J. KILGORE, G. ADAM;
Electrical and Computer Engin., The George Washington Univ., Washington, DC

Abstract: The brain exemplifies low-power robust computation and learning. This efficiency and robustness have been partly attributed to the wide diversity of neuron subtypes and corresponding connections. This creates a challenge for simulating these models: It remains unclear which mathematical representation can accurately replicate biological recordings. While previous work has focused on the computational complexity and range of model activity, a comprehensive comparison of model tunability towards biological baselines is still needed. In this work, we present a novel tuning methodology which allows for comparing the tunability of models. Our methodology incorporates a hyperparameter optimizer and an objective function that emphasizes mirroring behavior classification, spike count, and spike timing. Results demonstrate successful tuning of a 4-parameter Izhikevich model to match an example set of multi-level input current data for a range of granule cell ages (Fig. 1). We find our methodology produced neuron models that show equal firing patterns, e.g. non-adaptive spiking (NASP), and identical firing counts, but there remained a non-zero Van Rossum distance in spike timing. Additionally, we were able to tune multiple model types utilizing the same tuning protocol, demonstrating a model agnostic approach based purely on spiking activity. This work provides a foundation that can expand toward neuromorphic implementations and other applications where a computationally efficient neuron model needs to mirror biological behavior.

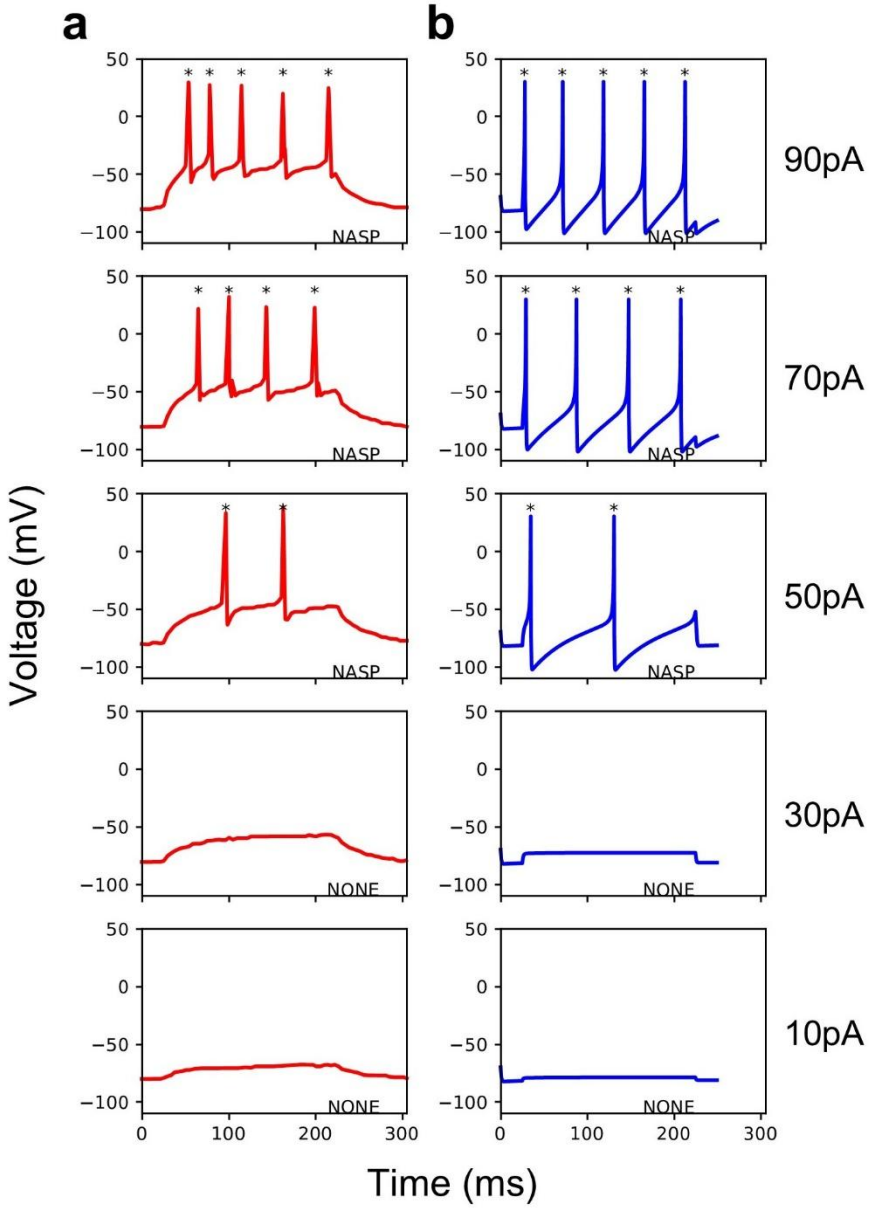


Figure 1. Example voltage traces of mature granule cell at 5 input current levels (a) and corresponding tuned 4-parameter Izhikevich model created with our novel tuning methodology (b).

Disclosures: J. Kilgore: None. **G. Adam:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.15/LL49

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

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NIH Grant R01NS122742
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María de Maeztu CEX2021-001164-M
Ramón y Cajal Fellowship RYC2022-035106-I
Excellence Cluster on Bilateral AI of the Austrian Science Fund 10.55776/COE12

Title: Deep-learning-assisted simulation of a cortical circuit: biological constraints as selectors of functionally equivalent solutions

Authors: *S. ITO[1], D. HAUFLER[1], J. GALVÁN FRAILE[2], K. DAI[1], J. AMAN[1], G. CHEN[3], C. MIRASSO[4], W. MAASS[5], A. ARKHIPOV[1];
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Abstract: We present a differentiable, GPU-accelerated simulation framework and a ~67,000-neuron point-neuron model of mouse primary visual cortex (V1) integrating electron-microscopy connectomics (MICrONS Consortium, Nature, 2025, www.microns-explorer.org), multipatch synaptic physiology (Campagnola, Seeman et al., Science, 2022, brain-map.org/connectivity/synaptic-physiology), cell-type-resolved intrinsic electrophysiology, and large-scale Neuropixels recordings across all cortical layers and 19 cell types. The model is stable at initialization from biological data, and backpropagation through time then optimizes synaptic weights to match in vivo activity statistics, while a Wasserstein regularizer preserves the experimentally measured synaptic weight distributions for each cell type pair.
Using this framework, we ask how strongly these wiring rules depend on the biological constraints on synaptic weights. We show that this is a non-trivial question, because statistics of cell-type-specific spontaneous and visually evoked neural activity are well reproduced without such constraints. Specifically, we trained matched models (N = 10 each) with the weight-distribution regularization removed and found that these unconstrained models remained stable and reproduced firing-rate and selectivity metrics indistinguishably from constrained models. Despite this functional equivalence, removing the constraints reshaped the synaptic organization: like-to-like excitatory and anti-like-to-like inhibitory motifs were disrupted, and some of the cell-type-specific connection pathways switched their tuning dependence entirely.
Thus, constraints from synaptic physiology act not merely as regularizers but as selectors among the many parameterizations that satisfy the same activity targets, guiding the circuit toward more

realistic cell-type-level wiring. This suggests a general strategy for bio-realistic modeling: use functional objectives to ensure realistic activity, incorporate biological constraints to shape realistic mechanisms, and use targeted constraint ablations to identify which constraints support which structural motifs.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.16/LL50

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

Support: Johns Hopkins Applied Physics Laboratory Independent Research & Development Program

Title: Synaptic Axonal Injury Signaling: Connecting the connectome to traumatic brain injuryusing mechanical and electrophysiological computational simulations

Authors: *A. S. LIAO, C. BRADFIELD, B. CELII;
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Abstract: Traumatic brain injury (TBI) is a common neurological disorder resulting from brain tissue deformation induced by head acceleration, leading to both acute and chronic symptoms. Even mild TBI can have lasting consequences; approximately 50% of patients with mild TBI do not return to their pre-injury level of neurobehavioral function within six months of injury (Maas *et al*, 2023). The cellular pathophysiology underlying mild TBI leading to the demonstrated behavior changes is unclear. One hypothesis is that TBI is a type of connectopathy, where damage to the underlying neurons and synapses manifests as changes in signaling through the neural network. To this end, the SYNaptic AXonal Injury Signaling (SYNAXIS) computational framework was developed to investigate how brain tissue deformation may alter neural connectivity. Using the MICrONS connectomics dataset, the SYNAXIS framework simulates tissue deformation, the resulting injury-induced changes in neuronal morphology, and downstream effects on electrophysiological activity. Mechanical perturbations based on head kinematics reconstructed from impacts sustained during professional football games (Sanchez *et al*, 2018, Newman *et al*, 2000) were used to estimate brain deformation with a finite element head model of a 50th percentile male. For concussive and sub-concussive cases, cortical strains at the continuum length scale were extracted and applied to skeletonized MICrONS neuron morphologies at the mesoscale. Strains were translated into injury by increasing neurite diameters, thereby modeling swellings along neurite segments analogous to focal axonal swellings, a hallmark pathology of TBI. Morphologies for multiple time points before and after the simulated injury were generated. A compartmentalized Hodgkin-Huxley model was

implemented for the control (unchanged morphology) case and injury cases to assess functional impacts of the injury-induced morphological changes. Impacts to action potential signal propagation was observed based on the number and diameter of swellings. The results suggest that injury-induced swellings could affect electrophysiological function. Future work will be explored to investigate how these shifts in action potential propagation could result in behavioral changes and how mechanical perturbations could affect other cellular mechanisms, such as changes to ion channel properties. The preliminary findings establish SYNAXIS as a potential *in silico* platform to investigate possible underlying cellular pathophysiological mechanisms to TBI-like mechanical impacts, which has been challenging to capture using conventional medical imaging techniques.

Disclosures: A.S. Liao: A. Employment/Salary (full or part-time):; Johns Hopkins Applied Physics Laboratory. **C. Bradfield:** A. Employment/Salary (full or part-time):; Johns Hopkins Applied Physics Laboratory. **B. Celii:** A. Employment/Salary (full or part-time):; Johns Hopkins Applied Physics Laboratory.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.17/LL51

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

Title: Transition pathways in whole-brain models: short-range vs long-range transitions in modeling human brain functional connectivity

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Abstract: The human brain exhibits spontaneous transitions between recurring resting-state activity patterns even without external input. Brain network models (BNMs), which incorporate individual anatomical connectivity into dynamical system models of neural population dynamics, provide a framework for studying how large-scale brain interactions generate these patterns. In such models, some brain states toward which neural activity evolves are called attractors in dynamical system terms. The presence of multiple attractors in the same system is known as multistability. Thus, multistable models allow spontaneous transitions between attractors, potentially supporting flexible switching between brain activity states. Previous work suggests that cross-attractor transitions better explain human resting-state functional connectivity (FC) patterns than within-attractor dynamics alone. However, the role of the unstable intermediate states—saddle points—remains unclear, despite their potential role in guiding the cross-attractor transitions. Specifically, it is unknown whether FC is driven mainly by direct neighboring transitions or by longer-range transitions across the landscape. To address this question, we used a whole-brain BNM constrained by Human Connectome Project (HCP) derived structural

connectivity. In the present study, attractors and intervening saddle points were identified using fixed point searches and perturbation analysis. The saddles were used to identify the transition path between attractors and the energy cost of the transition. Transition probabilities were determined by the energy cost of each transition and the relative contribution of long-range transition paths vs short-range transition paths. These transition probabilities are then used to compute the overall model FC as a weighted sum of FC associated with each transition. Our preliminary analysis indicates that when long-range transition paths are weighted more heavily, the model FC better captures human FC. This finding suggests that longer-range transitions across the attractor landscape capture dynamical organization beyond direct neighboring transitions alone. In the next step, we will validate this result statistically in a larger sample. This work provides an initial step toward linking global transition structure within the attractor landscape to empirical brain activity.

Disclosures: A. Das: None. **J. McLees:** None. **M. Zhang:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

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Program #/Poster #: PSTR291.19/LL53

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

Support: UH3NS103550
UH3NS141080
TL1TR002382
UL1TR002378
KL2TR002381

Title: Probing Subcallosal Cingulate Deep Brain Stimulation Mechanism Through Neural Mass Modeling of Local Field Potentials in Treatment Resistant Depression

Authors: *P. SARIKHANI[1], E. FITOZ[2], H. S. MAYBERG[5], R. J. BUTERA[3], C. ROZELL[4], S. ALAGAPAN[3];
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Abstract: Deep brain stimulation (DBS) of the subcallosal cingulate cortex (SCC) white matter has emerged as a promising intervention for treatment-resistant depression (TRD). Advances in neurotechnology enable longitudinal monitoring of local field potentials (LFPs) during DBS. Consistent with intraoperative and post-implantation findings, DBS acutely modulates beta-band activity. Prior evidence suggests SCC DBS exerts acute effects via projections to downstream dopaminergic and serotonergic targets, altering neurotransmitter concentrations and, in turn, neural activity. Notably, dopamine has been shown to modulate beta-band oscillations. However,

limitations in simultaneously measuring neurochemical and electrophysiological changes in vivo leave it unclear whether SCC DBS-induced LFP changes reflect the hypothesized neurochemical mechanisms. Neural mass models (NMMs) offer a principled approach to bridge this gap by linking measurable neural dynamics to interpretable parameters through biophysically grounded generative models. Combined with inference techniques, NMMs fitted to LFP signals can quantify DBS-induced changes in circuit-level properties and support hypothesis-driven exploration of neuromodulatory mechanisms. Here, we present a computational framework integrating the extended Jansen-Rit NMM with Stochastic Variational Inference (SVI) for principled Bayesian parameter estimation from LFP power spectral densities (PSDs). Three coupled neural populations were modeled, with neuromodulatory effects incorporated through concentration-dependent modulation of excitatory and inhibitory postsynaptic potential gains and the sigmoid threshold of the membrane potential-to-firing rate operator. Forward simulations revealed that the modulatory effects of serotonin and dopamine on oscillatory power were mutually dependent and nonlinear, with each neuromodulator's influence on oscillatory power contingent on the concentration of the other. The model was implemented in PyTorch, and the parameter inference was performed by optimizing the evidence lower bound (ELBO), with the likelihood defined as the log mean squared error between the simulated and observed LFP PSDs. To evaluate parameter estimation performance, synthetic LFP signals were generated from the Jansen-Rit model with known parameters. The SVI framework accurately recovered the PSDs, achieving a coefficient of determination of $R^2 = 0.99 \pm 0.005$ across five runs. When applied to experimental LFP data, the posterior mean PSD closely matched the empirical PSD, yielding R^2 of 0.88 ± 0.02 and a mean coverage of 0.99 within the 95% confidence interval.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.20/LL54

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

Support: NIH Grant R01AG092516

Title: Computational modeling of morphologically realistic axons provides novel insight into action potential conduction by cortical pyramidal cells

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Abstract: Reconstruction of highly complex pyramidal cell axons across long distances and branch orders is challenging, limiting the availability of anatomically realistic constraints for computational models. To derive branch-specific morphometric constraints relevant to conduction, we used Neuroglancer to manually trace and quantitatively measure 32 layer 3 pyramidal axons from the H01 human temporal cortex 3D electron microscopy dataset (Shapson-Coe et al., 2024). Of these, 21 cells possessed myelinated main axons, with a mean pre-myelination axon segment length of 217±30 μm. However, only 2 of 571 primary collaterals identified across the dataset were myelinated within the gray matter. Subsequent detailed analyses of a subset of 5 extensively reconstructed axons showed that primary collateral branch points were concentrated proximally, with most collaterals emerging within 500 μm of the soma. Mean main axon fiber (myelin + axon) and axon diameters were 0.90±0.03 μm and 0.63±0.03 μm, respectively. Primary and secondary collateral diameters averaged 0.20±0.004 μm and 0.17±0.006 μm. Because our computational models are based on rhesus monkey lateral prefrontal cortex pyramidal cells, confocal imaging and reconstruction of intracellularly filled monkey cells with excellent axon fills are being used to assess axonal topology and branch-order diameter relationships. Preliminary analyses suggest a similar branch-order diameter hierarchy to that observed in the H01 dataset, with main axon, primary collateral, and secondary collateral diameters of 0.73 μm, 0.41 μm and 0.39 μm, respectively. These anatomical measurements prompted revision of previously published multicompartment models in which both main axons and collateral branches were myelinated. Preliminary simulations incorporating empirically observed collateral diameter ratios revealed that action potential (AP) propagation was frequently disrupted in models with myelinated collaterals. Across a cohort of 50 models, collateral propagation failure occurred in 56-70% of models, depending on g-ratio. In contrast, models incorporating unmyelinated collaterals, consistent with H01 observations, exhibited reliable AP propagation across all branches in all 50 models. Ongoing analyses are investigating the biophysical mechanisms underlying these differences and the sensitivity of collateral conduction to branch-specific ion channel densities. Together, these findings suggest that realistic collateral geometry and differential myelination of main axons and collateral branches are important determinants of AP conduction and propagation reliability in cortical pyramidal cells.

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Poster

PSTR291: Modeling Neural Systems Across Scales

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.21/LL55

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

Support: PAPIIT (DGAPA-UNAM) 200126
SECIHTI CVU 1177488

Title: A computational approach on the contribution of Calcium channels in shaping orthodromic transmission in striatal direct and indirect pathway neurons

Authors: *M. GARCIA MATA[1], A. LAVILLE[2], D. TAPIA[3], E. GALARRAGA[4], J. BARGAS[5];
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Abstract: Calcium channels are essential regulators of neuronal excitability and synaptic integration. In striatal projection neurons (SPNs), direct (dSPNs) and indirect (iSPNs) pathways exhibit distinct firing dynamics when stimulated orthodromically from cortex or thalamus, including differences in polysynaptically driven plateau potentials and the duration of spike trains (Flores-Barrera 2010). Understanding how specific calcium channel subtypes contribute to these differences is important. Experimentally, critical differences have been found on T-type, L-type, and N/PQ-type calcium channels functions between dSPNs and iSPNs (Arias-Garcia 2013, Vizcarra-Chacon 2013, Garcia-Vilchis 2019). Here we use computational models to reproduce their different orthodromic responses in trying to understand the anatomical and ion channels constraints that explain them. Dendritic T-type channels facilitated plateau potentials in dSPNs neurons but shortened responses in iSPNs neurons by generating fast repolarizations. L-type channels provided calcium influx to sustain the plateaus. In contrast, N/PQ channels contributed to synaptic coupling through localized dendritic calcium domains that activate SK/BK potassium channels whose function is to control both duration and amplitude of polysynaptic plateau potentials and spike trains. The model was capable to reproduce previous experimental observations through physiologically consistent conductance adjustments. Our computational approach demonstrates that calcium channel diversity is a key determinant of orthodromic transmission in the SPNs of both basal ganglia pathways. Redistributing different calcium currents the model captures pathway-specific dynamics while maintaining ion conductances within physiological ranges. These findings emphasize the importance of intrinsic channel-specific contributions in shaping striatal synaptic responses. Noticeably, these conductances are highly modulated by transmitters via G-protein coupled receptors, whose actions on orthodromic responses can in turn be modeled.

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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

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Program #/Poster #: PSTR291.22/LL56

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

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CNPq Grant 315055/2025-1
CAPES-PROBAL Grant 88887.161300/2025-00
NIH Grant U24EB028998

Title: Human Cortical Microcircuit Modeling from a Petavoxel Fragment of Cerebral Cortex

Authors: *F. S. BORGES[1,2,3], D. L. M. SOUZA[1], T. KHASHAN[4], S. DURA-BERNAL[4,5]; [1]State Univ. of Ponta Grossa, Ponta Grossa, Brazil; [2]UFABC, São Paulo, Brazil; [4]Physiol. and Pharmacol., [3]SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; [5]Ctr. for Biomed. Imaging and Neuromodulation, Nathan Kline Inst. for Psychiatric Res., New York, NY

Abstract: The functions of the central nervous system emerge from interactions among neurons distributed across brain regions. These interactions generate patterns of neural activity that can be measured with electrophysiological recordings such as local field potentials (LFP) and electroencephalography (EEG). In neurological disorders, cellular and synaptic alterations reshape these activity patterns, yet it remains challenging to determine experimentally how microscale pathology combines to produce macroscale changes in human cortical dynamics. Mechanistic biophysical models can help bridge this gap by linking disease-related cellular and synaptic changes to circuit-level dysfunction. Here, we develop a biophysically detailed human cortical model in NetPyNE/NEURON constrained by nanoscale reconstruction of a petavoxel-scale fragment of human cerebral cortex comprising over 15,000 neurons and 150 million synapses. The model includes morphologically and biophysically detailed pyramidal neurons and SST, PV, and VIP interneurons, incorporating active membrane conductances, short-term synaptic plasticity, background synaptic fluctuations, cell-type-specific connectivity rules, and structured excitatory-inhibitory architecture. First, we apply AI-assisted morphology correction and fit single-neuron electrophysiological properties using human experimental data. Second, we build and optimize a Layer 2/3 microcircuit (1,000 simulated neurons) to reproduce cell-type-specific firing patterns and LFP/EEG signatures. Finally, we extend the model toward a full cortical column and examine circuit responses across stimulation and state conditions, including sleep-like and wake-like background activity and external perturbations such as DBS, TMS, and tACS. Future work will validate the full column model against human TMS-EEG data, simulate AD-relevant EEG signatures, optimize stimulation parameters, and incorporate aging and patient heterogeneity. This approach may support mechanistically interpretable biomarkers for disease diagnosis and more precise planning of personalized brain-stimulation protocols.

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Poster

PSTR291: Modeling Neural Systems Across Scales

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Program #/Poster #: PSTR291.23/LL57

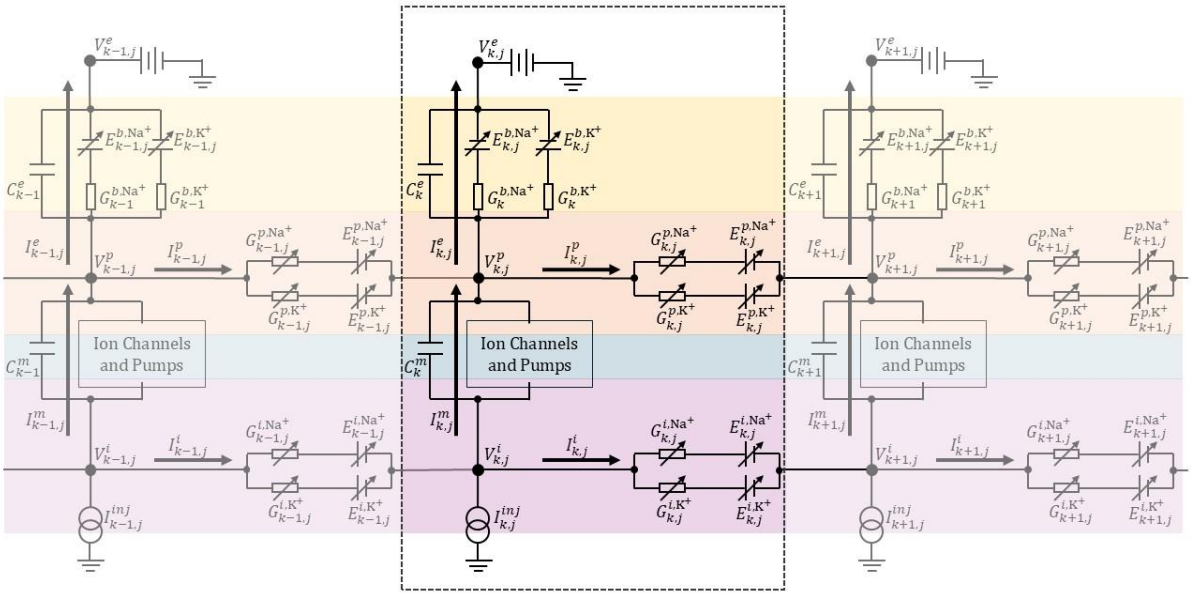
Topic: J.06. Computation, Modeling, and Simulation

Support: 1R01NS146406-01
R01NS110893

Title: Beyond standard cable theory: An optimized Nernst-Planck framework for axonal electrodiffusion simulations

Authors: *D. KOPALA[1], G. FOXWORTHY[2], G. FRIDMAN[3];
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Abstract: Standard axonal conduction simulation software, such as NEURON, has long served as the bedrock of computational neuroscience. However, standard cable theory implementations fall short when evaluating external long-duration stimulation, where lasting electric fields interact with local ion gradients. To address this, we engineered an independent, optimized computational framework that shifts axonal modeling from simple Fick diffusion to comprehensive Nernst-Planck electrodiffusion. Standard modeling environments utilize a fixed, non-ion-specific longitudinal conductivity and isolate longitudinal currents from compartmental concentration calculations. In contrast, our model treats longitudinal conductivity as an ion-specific, time-dependent variable driven by local concentration dynamics, forcing all intra-axonal and periaxonal currents to directly modulate local ion pools. Additionally, our framework enables direct, high-resolution control over external fields by providing a custom stimulation interface. To capture the microenvironment of myelinated fibers, we integrated detailed structural variations including nodal constrictions, paranodal loops, and the periaxonal space. To manage the massive increase in interdependent variables without severe performance degradation, we developed a custom solver optimized for minimal overhead and rapid execution. Our results demonstrate that coupled electrodiffusive variations significantly alter predicted axonal responses to external fields, highlighting the necessity of precise electrochemical modeling.



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Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

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Program #/Poster #: PSTR291.24/LL58

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

Support: NIH Grant 1RF1NS132812-01

Title: High-resolution simulation of auditory space-specific neurons in the barn owl

Authors: *J. M. R. FOX[1], B. J. FISCHER[2], W. M. DEBELLO[3], D. FIORAVANTE[4], M. H. ELLISMAN[5], J. L. PENA[6];
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Abstract: The barn owl (Tyto alba) sound localization system provides a powerful model for studying sensory neural computation. Recent anatomical studies of auditory space-specific neurons (SSNs) in the owl inferior colliculus have revealed unusually complex postsynaptic

structures, termed toric spines because of their distinctive looping morphology. Toric spines are hypothesized to contribute to the integration of sound frequency and binaural cues, but their computational role remains unknown. Realistic modeling of SSNs has been limited by the difficulty of converting high-resolution anatomical reconstructions into simulation-ready morphologies. To address this challenge, we developed MASCAF, a software pipeline that robustly fits complex neuronal and spine geometries for multi-compartmental simulation. MASCAF enables the generation of high-resolution morphologically accurate models from microscopy reconstructions while preserving geometric features critical to electrical signaling. Using MASCAF and the Arbor simulation framework, we construct detailed multi-compartment models of SSNs constrained by anatomical measurements and electrophysiological data. Combined with realistic and variable models of presynaptic input, these simulations enable systematic investigation of signal propagation, electrical compartmentalization, local voltage amplification, nonlinear synaptic integration, and action-potential generation in the parent neuron. By varying passive and active membrane properties, we quantify how morphology and membrane mechanisms shape neural responses and evaluate the extent to which toric spines function as independent computational subunits. This work establishes the first computational framework for studying toric spine function and provides a quantitative approach for investigating sensory integration in the barn owl auditory system.

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Poster

PSTR291: Modeling Neural Systems Across Scales

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Program #/Poster #: PSTR291.25/LL59

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

Support: AMED Brain/Minds 2.0 (JP25wm0625406, JP26wm0625406)
MEXT Program for Promoting Research on the Supercomputer Fugaku (hp250231)
HPCI System Research Project (hp260155)

Title: Evaluating the reproducibility and interoperability of Neulite with existing neuron simulators

Authors: K. T. AKIRA, R. KURIYAMA, T. MURANAKA, H. SUGIMOTO, ***T. YAMAZAKI**;
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Abstract: Neulite is a lightweight neuron simulator designed for biophysically detailed neuron and network models (Kuriyama et al., 2025). It works closely with the Brain Modeling ToolKit (BMTK), a Python package developed by the Allen Institute (Dai et al., 2020). Models built with

BMTK's "bionet" module and executed on the NEURON simulator can run on the Neulite kernel by using the "bionetlite" module, which serves as a drop-in replacement for bionet. Therefore, the NEURON-based and Neulite-based implementations within BMTK should yield identical simulation results. In this study, we examined the reproducibility of simulation results between these two versions. However, while Neulite currently supports only neuron models registered in the Allen Cell-Types Database, NEURON accommodates a much wider variety of models, such as the mouse primary motor cortex model (Dura-Bernal et al., 2023). To address this limitation, we also explored methods for implementing non-BMTK models on the Neulite kernel, aiming to ensure interoperability between NEURON and Neulite. To evaluate reproducibility, we used the Allen V1 model (Billeh et al., 2020) and compared the firing rates of individual neuron populations in response to constant current inputs. By aligning the temporal resolution and numerical methods, we obtained quantitatively comparable results. Furthermore, we found that performing parameter fitting enhanced the reproducibility of the voltage traces. Regarding interoperability, we leveraged large language models (LLMs) to translate NMODL files into C code for Neulite and to perform parameter fitting, which yielded qualitatively comparable results for individual neurons in the mouse primary motor cortex. In conclusion, although additional parameter tuning is required, Neulite is capable of generating numerical results close to those of NEURON.

Disclosures: K.T. Akira: None. **R. Kuriyama:** None. **T. Muranaka:** None. **H. Sugimoto:** None. **T. Yamazaki:** None.

Poster

PSTR291: Modeling Neural Systems Across Scales

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR291.26/LL60

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

Support: UCSB Chancellor's Fellowship

Title: Parameter identifiability in neural circuit models reveals low-rank subcircuits underlying robust computation

Authors: *A. BERTICS[1], F. DINC[2], E. DEPONNAT[3], B. KURTKAYA[2], P. YUAN[4], N. MIOLANE[2];
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Abstract: Both biological and artificial neural networks suffer from parameter non-identifiability, in which vast regions of synaptic-weight space correspond to models with indistinguishable outputs. This degeneracy is a fundamental obstacle to interpreting dynamical models of neural computation, because networks that implement the same computation can place very different weights on certain connections, producing biologically uninterpretable parameter

estimates and unconstrained out-of-distribution dynamics. In this work, we develop a theory of parameter identifiability for a broad class of recurrent neural network models, characterizing the identifiable parameter subspaces that govern the observed task-relevant dynamics. We find that the identifiable parameters correspond to the low-rank components of the parameter matrices, and that by magnitude they only account for small fraction of synaptic weight. Despite their apparent weakness, these connections define latent subcircuits whose task-relevant dynamics are invariant across many parameter configurations consistent with the data. Targeted perturbations along the non-identifiable directions expose additional subcircuits, whereas perturbations along the identifiable directions yield the least new information. Finally, we introduce a principled procedure for training data-constrained models, in which digital twins are trained to reproduce observed neural activity, by restricting parameter optimization to identifiable subspaces. Together, our results show that robust, task-relevant computation is encoded in sparse, weakly coupled latent subcircuits embedded within a larger, redundant connectome, and provide practical guidelines for isolating this structure directly from data.

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Poster

PSTR292: Principles of Neural Computation

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Program #/Poster #: PSTR292.01/LL61

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

Support: JST SPRING, Grant Number JPMJSP2110
JSPS KAKENHI Grant Number 24K15104
AMED-CREST 26gm1510005s0206

Title: Biologically Plausible Continual Learning through Metaplastic Regulation of Hebbian and Anti-Hebbian Plasticity

Authors: *A. TOMOTO, J.-N. TERAMAE;
Kyoto Univ., Kyoto, Japan

Abstract: Continual learning concerns how a system can sequentially adapt to new tasks or contexts while preserving previously acquired representations. In addition to its importance for machine learning applications, continual learning provides a framework for understanding the biological mechanisms underlying memory storage and adaptation. However, conventional approaches rely on global error-based optimization (Kirkpatrick et al., 2017) or the permanent freezing of synaptic connections to preserve memories (Xiao et al., 2024), limiting their biological plausibility. Consequently, it remains unclear how memories can be formed, maintained, and modified across multiple contexts using only local neural activity and synaptic plasticity. To address this question, we propose a simple two-layer neural network that combines

Hebbian and anti-Hebbian plasticity for learning input statistics with homeostatic metaplasticity that regulates learning rates in an activity-dependent manner. We show that the model learns the dominant directions in the input signals through Hebbian plasticity, while anti-Hebbian lateral inhibition reduces redundancy among output neurons (Foldiak et al., 1990; Pehlevan et al., 2015). Homeostatic metaplasticity acts as an activity-dependent gate on Hebbian plasticity, reducing the Hebbian learning rate to consolidate connections associated with active neurons while allowing less active neurons to regain synaptic plasticity. We further clarify the relationship among the rank of the input covariance matrix, the number of output neurons, and the number of stored contexts. We also identify a significant trade-off between memory retention and robustness to noise, governed by the metaplasticity threshold. These results provide a minimal biologically plausible framework for studying the stability-plasticity dilemma in continual learning, where the acquisition of new memories must be balanced against the preservation of existing representations. More broadly, our work extends the study of continual learning beyond task-performance preservation by proposing a local circuit mechanism that enables representations to evolve across changing contexts.

Disclosures: A. Tomoto: None. **J. Teramae:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.02/LL62

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

Support: NIH Grant R01 DC007683

Title: Coordination of Articulation and Voicing in Speech Motor Control: A Coupled CT-RNN Approach

Authors: *R. ZAVERI[1,2], L. BULLOCK[4,5], G. CLER[6,7], F. H. GUENTHER[3,1,8];
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Abstract: Effective coordination between articulation and voicing is essential for fluent speech production, and a breakdown in this coordination may contribute to disorders such as stuttering. In recent years, experimental and theoretical approaches have yielded a wealth of information regarding the neural mechanisms underlying motor preparation and execution. The goal of the current study is to develop a theoretical framework for generalizing these findings from the primate motor control literature to speech in humans, and to investigate the possibility that discoordination between articulatory and vocal networks may underlie stuttering, a disorder

characterized by an impaired ability to initiate word motor programs (Guenther et al., 2026, preprint).
To this end, we implemented continuous-time recurrent neural networks (CT-RNNs) involving two cross-coupled sub-networks: a voicing network and an articulation network. We used a publicly available articulometry/acoustic dataset, mngu0 (Korin et al., 2011, Interspeech), to train the model on a delayed word production task. The networks were trained with standard backpropagation through time. During testing, various perturbations were applied to the latent spaces of the two sub-networks to disrupt coordination. Analyses reported here focused particularly on the transition period from preparatory activity during the delay period to movement onset.
Our dynamical systems analysis revealed several key findings. First, despite not constraining the network to develop orthogonal latent subspaces in the preparatory and execution periods, network solutions tend toward such orthogonality, as previously reported for motor cortical activity for arm movements in primate motor cortex (Elsayed et al., 2016, Nature). Second, the transition period between the preparatory and movement phases exhibits ramp-like (monotonically increasing or decreasing) behavior in latent neural trajectories, shifting towards stable attractor states for movement onset. Third, the transition period can be influenced by the degree of synchrony between the articulatory and voicing sub-networks. Perturbation of this synchronization can cause the network to fail to remain in an appropriate energy well, leading to transient motor readouts.
Overall, our CT-RNN simulations provide a “proof of concept” that poorly coordinated activity across articulatory and vocalic networks can lead to stuttering-like behaviors. Future work will compare model simulations to human motor cortical recordings during attempted speech in anarthric participants of the Braingate2 Clinical Trial (ClinicalTrials.gov identifier: NCT00912041).

Disclosures: R. Zaveri: None. **L. Bullock:** None. **G. Cler:** None. **F.H. Guenther:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.03/LL63

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

Support: Kakenhi 22K18662
JSPS Overseas Research Fellowships

Title: SNr activity deviation minimization enables multi-context reinforcement learning in a cortico-basal ganglia circuit model

Authors: *K. HIROKANE[1], K. KUBO[2], T. YOSHIDA[2], R. TAKEHARA[2], T. KITSUKAWA[2]; [1]MIT, Cambridge, MA; [2]Col. of Life Sci., Ritsumeikan Univ., Kusatsu, Japan

Abstract: Animals flexibly adapt their behavior across many environments, yet how the cortico-basal ganglia circuit implements this flexibility through reinforcement learning remains unclear. Dopamine neurons encode a reward prediction error resembling a temporal-difference (TD) error, and striatal neurons correlate with state and action value, but these findings describe the circuit's learning signals rather than the organizing principle that enables learning across many contexts. Anatomically, the cortico-basal ganglia circuit is organized as parallel, topographically ordered loops, and within each loop the direct, indirect, and hyperdirect pathways project over characteristically different ranges. We asked whether this modular, topographic organization with segregated projection ranges could itself implement the computations necessary for flexible reinforcement learning across many contexts. To test this, we built a network of neocortex-basal ganglia modules tiled horizontally following the shared topography of cortex and basal ganglia. Each module corresponds to one position within a maze, and inter-module connections reflect the differing projection ranges of the three pathways, naturally implementing TD-error computation through lateral signaling between modules. We further proposed that this closed loop, driven by dopamine-dependent plasticity, acts to minimize the deviation of SNr activity from its average level. We formalized this as an energy function and showed analytically that the circuit performs gradient descent on it, simultaneously updating synaptic weights and cortical activity through SNr-to-cortex feedback. This update rule is biologically realizable through known dopamine-dependent plasticity at corticostriatal and cortico-STN synapses, consistent with the disrupted control seen when SNr output is dysregulated in Parkinson's and Huntington's disease. The model learned up to 100 distinct maze layouts, and as learning progressed, SNr activity deviation and total circuit energy fell, indicating circuit stabilization. The cortex spontaneously developed distinct, stable activity patterns for each context through learning alone, with no external label distinguishing environments, suggesting context representations emerged through the circuit computation itself. These results suggest that the topographic, modular organization of the cortico-basal ganglia circuit, combined with SNr activity-deviation minimization, supports flexible multi-context behavior by forming stable, context-specific cortical representations.

Disclosures: K. Hirokane: None. **K. Kubo:** None. **T. Yoshida:** None. **R. Takehara:** None. **T. Kitsukawa:** None.

Poster

PSTR292: Principles of Neural Computation

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.04/LL64

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

Support: JSPS KAKENHI, JP23K19415, JP25K18569, JP23KJ0666, JP23H05476, JP25K24466
JST ACT-X, JPMJAX25LI, JPMJAX25CA
JST BOOST, JPMJBS2418
JST CREST, JPMJCR23N2

RIKEN Center for Brain Science
RIKEN TRIP initiative (RIKEN Quantum)

Title: A model of schema and compositional learning based on biological dimensionality reduction during sleep

Authors: *K. YOSHIDA[1], G. SHIMIZU[1,2], Y. KINOSHITA[1,2], K. INOKUCHI[3], T. TOYOIZUMI[1,2];
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Abstract: Reorganizing learned knowledge into generalized representations and using them to support future learning are essential aspects of cognition, often described as schema formation and use. Sleep has been considered to contribute to schema formation by promoting memory reorganization. However, the computational and circuit mechanisms underlying these processes remain unclear. Here, we propose a theoretical model in which schemas emerge through the formation and alignment of low-dimensional neural representations. In this model, high-dimensional input patterns are reorganized into low-dimensional manifolds through replay-driven Hebbian nonlinear dimensionality reduction. This learning rule organizes high-dimensional inputs into low-dimensional manifolds that retain the similarity structure of the original patterns. Manifold alignment then maps representations with shared task structure onto a common format, enabling downstream readout circuits to be reused across tasks. Through this process, new experiences are transformed into low-dimensional representations that preserve relational structure while integrating with previously acquired schemas. The model captures three core features of schema learning: rapid learning of similar tasks by reusing low-dimensional representations from prior experience, sleep-dependent generalization to unobserved relationships in transitive inference, and compositional recombination of schemas to solve novel tasks. These results are consistent with multiple experimental observations and generate predictions about how the brain forms schemas and uses them to support future learning. Together, our findings suggest a potential neural mechanism for forming, aligning, and recombining low-dimensional schemas.

Disclosures: K. Yoshida: None. **G. Shimizu:** None. **Y. Kinoshita:** None. **K. Inokuchi:** None. **T. toyoizumi:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.05/LL65

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

Support: Army Research Labs Grant W911NF-26-1-A006

Title: Bias-Driven Reconfigurable Computation in Hardware-Agnostic Neural Circuits

Authors: *A. J. WHITE[1], C.-C. LO[2], B. LIU[3], K.-A. WU[4], M.-J. HSIEH[2];
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Abstract: Biological neural circuits adapt rapidly to diverse stimuli, far faster than synaptic plasticityallows, implying circuits can switch function without changing synaptic weights. We identify ahyper-flexible 4-neuron circuit, comprising a recurrent excitatory loop coupled to a recurrentinhibitory loop. An underlying double-cusp bifurcation enables reconfiguration via bias currentsalone, no changing of the synaptic weights. Moreover, this circuit is hardware-agnostic,generalizing across spiking and non-spiking implementations.As a demonstration of reconfigurability, we classify CRIREL outputs across 24 unique logicalfunctions, eight nontrivial logic gates (AND,OR, XOR, NAND, NOR, NXOR, IMP, NIMP)under magnitude, timing, and phase input modalities. Moreover, balanced trinary gates (-1,0,+1)can also be realized in the same 4-neuron circuit. Learning can further stabilize gate selectionunder noise.As proof of concept, we implement a motion-detection model in which the circuit uses motorcommands to reconfigure receptive fields, detecting motion against optical flow and generatingevent-based surprise signals.

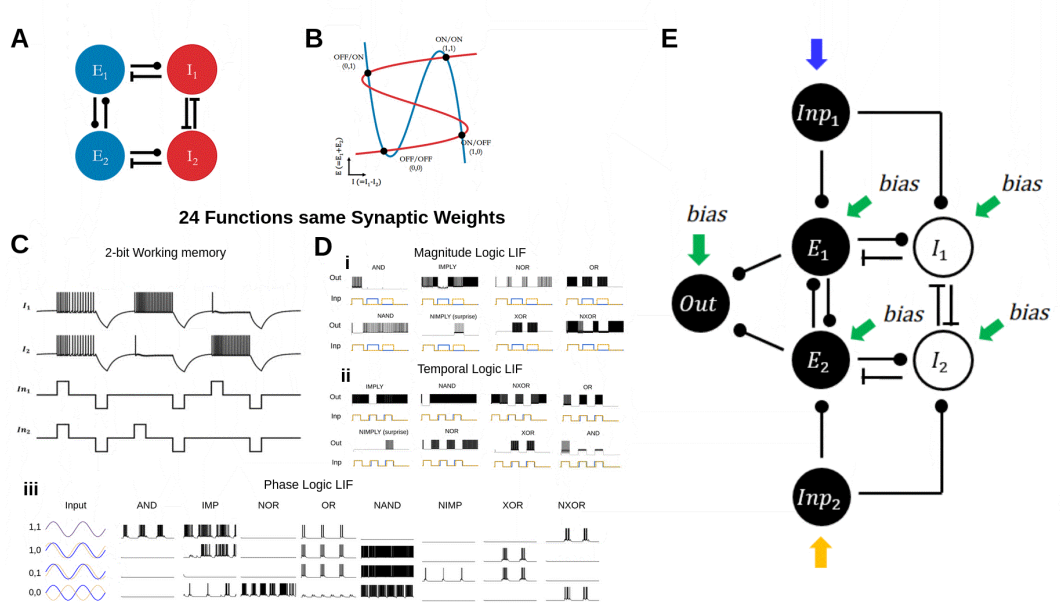


Figure1. TheCRIREL circuit. A)Circuit diagram of the 4-neuron circuit. B)2-D reduced phase plane;bluenullcline = excitation, red = inhibitory;supports 2-bit working memory. C)LIF implementation storing ON/ON,ON/OFF, OFF/ON, or OFF/OFF until reset. D)Twenty-four unique functions under fixed synaptic weights acrossmagnitude (Di), timing (Dii), and phase (Diii)input modalities. E)Full neuromorphic logic gate circuit;inputneurons convert pulses to spikes but are not essential to circuit computation.[1]Liu, B., White, A.J. and Lo, C.C., 2025. Augmenting flexibility:mutual inhibition between inhibitory neurons expandsfunctional diversity. *iScience*, *28*(2).[2] White, A.J., Liu, B., Hsieh, M.J., Chang, M.F., Wu, K.A. and Lo, C.C., 2025. Hyper flexible neural networks rapidly switchbetween logic operations in a compact four neuron circuit. *npjUnconventionalComputing*, *2*(1),p.2.

Disclosures: A.J. White: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Taiwan Patent No. #I725914 and United States Patent No. #US12079709B2. **C. Lo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Taiwan Patent No. #I725914 and United States Patent No. #US12079709B2. **B. Liu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Taiwan Patent No. #I725914 and United States Patent No. #US12079709B2. **K. Wu:** None. **M. Hsieh:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.06/LL66

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

Support: Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 24K15104
Japan Agency for Medical Research and Development (AMED) AMED-CREST 26gm1510005s0206

Title: Information-theoretic principles governing engram cell allocation in the hippocampus

Authors: *K. CHIBA[1], J.-N. TERAMAE[2];
[1]Informatics, [2]Kyoto Univ., Kyoto, Japan

Abstract: Recent developments in experimental techniques have enabled the identification of engram cells, a subset of neurons that are selectively activated during specific environmental contexts and constitute the cellular substrate of episodic memory. While it has remained unclear which neurons are recruited as engram cells, a recent study showed that a subset of CA1 place cells, which are widely believed to constitute a neural substrate of spatial memory, are recruited as engram cells by expanding their place fields to represent contextual information specific to individual environments. This finding indicates a trade-off between spatial information represented by place cells and contextual information represented by engram cells. However, the principle governing this trade-off and determining what fraction of place cells are recruited as engram cells remains unclear. To address this fundamental question, we develop an information-theoretic framework to quantify the trade-off between spatial and contextual information encoded by CA1 neurons. By optimizing this trade-off, we determine the fraction of place cells recruited as engram cells as a function of the probability that an animal experiences each context. The theory provides nontrivial yet biologically plausible predictions. First, the optimal fraction of engram cells undergoes a discontinuous transition from zero to a finite value when the corresponding context probability exceeds a critical threshold. Second, the optimal fraction is maximized at an intermediate context probability and decreases as the context probability becomes large. Furthermore, we analytically derive the critical context probability as a function

of the strength of contextual input and the relative weight of contextual information. These results provide a general theoretical principle governing engram cell allocation and offer experimentally testable predictions.

Disclosures: K. Chiba: None. **J. Teramae:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

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

Support: NIH/NIDCD Grant R01DC018227
NIH/NIDCD Grant R01DC022610
American Association of University Women (AAUW) International Fellowship
NIH/NGM Grant K12GM102778

Title: Probing neural mechanisms of taste discrimination learning with recurrent neural networks

Authors: *L. LANG[1], Y. ZHENG[1], J. BLACKWELL[2], L. GIANCARLO[1], A. FONTANINI[1]; [1]Stony Brook Univ., Stony Brook, NY; [2]Neurosci., Brown Univ., Providence, RI

Abstract: The gustatory cortex (GC) produces dynamic patterns of activity that are critical for mediating taste-based decision-making. Specifically, recent work has shown GC's involvement in a taste mixture-based perceptual decision-making task where mice are required to lick in one of two directions based on the predominant taste mixture component. Behavior in the context of this task is supported by both GC linear activity (encoding of a mixture component's relative concentration in a graded fashion) and categorical activity (encoding of perceptual categories or choices in a binary fashion). Furthermore, this GC activity is plastic; training on increasingly difficult mixture pairs leads to improved task performance, called discrimination learning, which is accompanied by neural changes including increased categorical activity. The circuit-level neural mechanisms underlying the changes observed in GC with discrimination learning are unknown. Here we use a recurrent neural network (RNN)-based modeling approach to investigate the potential circuit-level mechanisms. For each test session, we train an RNN to match the experimentally observed psychometric performance curve to obtain a pre-learning model, then continue training the network until performance reaches pre-determined discrimination learning criteria to obtain a corresponding post-learning model. We find that post-learning models are associated with population-/network-level changes including increased mean firing rate and an earlier transition from predominantly linear to predominantly categorical activity. Post-learning models are also associated with parameter changes at the single neuron/synapse level including increased mean synaptic weight and neural bias. In order to integrate these multilevel changes with a mechanistic explanation, ongoing research is focused

on additional discrimination learning simulations with freeze constraints on different subsets of trainable parameters.

Disclosures: L. Lang: None. **Y. Zheng:** None. **J. Blackwell:** None. **L. Giancarlo:** None. **A. Fontanini:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.08/LL68

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

Title: Why Mesoscale? A Closed Form Theory of Temporal Averaging and Neural Decoding

Authors: *H. AHMED[1], T. SAMIEI[2], E. NOZARI[3];
[1]UCR, Riverside, CA; [2]Univ. of California, Riverside, CA; [3]Mechanical Engin., Univ. of California, Riverside, Riverside, CA

Abstract: Why Mesoscale? A Closed-Form Theory of Temporal Averagingand Neural DecodingHafiz Fareed AhmedToktam SamieiErfan NozariAbstractWhile neural activity is organized across multiple temporal scales, the principles that deter-mine the accuracy and fidelity of neural information representation across such scales remainunclear. In recent empirical work [1], we showed that decoding performance in large-scale neuralrecordings is maximized at intermediate, mesoscopic temporal resolutions. However, the theo-retical principles underlying this mesoscale optimality remain unknown. Here, we develop ananalytical framework to determine how temporal integration shapes neural information repre-sentation across scales in relationship with signal and noise correlations.We model neural population activity as temporally structured signal corrupted by correlatednoise, and derive closed-form expressions for information representation (d-prime) at micro-scopic, mesoscopic, and macroscopic temporal resolutions. Using this framework, we systemat-ically characterize how temporal correlations in both signal and noise govern the effects of tem-poral averaging on information representation. Our analysis reveals two distinct regimes. Whensignal correlations remain persistent over time while noise correlations decay, temporal integra-tion favors one of the two extremes—microscopic or macroscopic representations—dependingon the relative strengths of signal and noise correlations. In contrast, when both signal andnoise correlations decay with temporal separation, temporal integration produces a nontriv-ial trade-off. Moderate integration suppresses noise while preserving coherent signal, whereasexcessive integration mixes weakly related signal components and degrades representationalstructure. Under these biologically realistic conditions, mesoscopic representations emerge asoptimal across broad parameter regimes. Thus, our theory identifies the correlation structuresunder which mesoscale averaging maximizes d-prime.Overall, our results provide a theoretical explanation for previously observed mesoscale opti-mality in neural decoding and establish temporal integration as a principled mechanism linkingmultiscale neural dynamics to information representation.[1]

Samiei, T., Zou, Z., Imani, M. and Nozari, E., 2024. Optimal decoding of neural dynamicsoccurs at mesoscale spatial and temporal resolutions. Frontiers in Cellular Neuroscience, 18,p.1287123.1

Disclosures: H. Ahmed: None. **T. samiei:** None. **E. Nozari:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

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Program #/Poster #: PSTR292.09/LL69

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

Support: STI2030-Major Projects (no. 2022ZD0204900)
Beijing Major Science and Technology Project (no. Z251100008425003)
NSFC Projects (no. 62406160 and 32021002)

Title: Spacing effect improves generalization in biological and artificial systems

Authors: *G. SUN;
IDG/McGovern Inst. for Brain Res., Tsinghua Univ., Beijing, China

Abstract: Generalization is a fundamental criterion for evaluating learning effectiveness, a domain where biological intelligence excels yet artificial intelligence faces challenges. In biological learning and memory, the well-documented *spacing effect* shows that appropriately spaced intervals between learning trials significantly improve behavioral performance. While multiple theories have been proposed to explain its underlying mechanisms, one compelling hypothesis is that spaced training promotes integration of input and innate variations, thereby enhancing generalization to novel but related scenarios. Here we examine this hypothesis by introducing a bio-inspired spacing effect into artificial neural networks, integrating input and innate variations across spaced intervals at neuronal, synaptic, and network levels. These spaced ensemble strategies yield significant performance gains across benchmark datasets and network architectures. Biological experiments on *Drosophila* further validate the complementary effect of appropriate variations and spaced intervals in improving generalization, which together reveal a convergent computational principle of biological learning and machine learning.

Disclosures: G. sun: None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.10/LL70

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

Support: NIH DIRP ZIAMH002797

Title: Emergence of "Gliders" in cellular-automaton-based balanced E-I networks

Authors: *M. BELLUSCIO, S. PAJEVIC, D. PLENZ;
Section on Critical Brain Dynamics, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Coherent propagating structures (gliders), well-characterized in cellular automata, are suggested information carriers in those systems. Here we assess whether gliders serve an analogous role in excitatory-inhibitory (E-I) recurrent neural networks using a spatially homogeneous model and rate coding. The 2-layer neuronal automaton comprised a toroidal excitatory layer (100×100; S_{EE}) and inhibitory layer (50×50; S_{II}), each symmetrically connected to their eight nearest neighbors. Cross-layer interactions consisted of symmetric feedback inhibition (S_{IE}) and asymmetric feedforward excitation (S_{EI}). The 4:1 E:I density ratio enforced locally asymmetric but globally homogeneous connectivity. Network dynamics evolved via a sigmoid-like rectifying transfer function onto [0,1]. Activity was sustained by recurrent stochastic binary drive to a central 12×12 region of the excitatory layer when population activity fell below a minimal threshold. Systematically varying global E-I synaptic strengths, we identified spontaneous glider formation in a narrow parameter regime near E-I balance, at the transition between excitation- and inhibition-dominated dynamics. Although the model produced diverse glider types, one dominant glider emerged consistently across parameter space, enabling analytical characterization of its dynamics and artificial reintroduction into the network. Simulated glider-glider collisions and noisy conditions confirmed stability and robustness within specific parameter regions. To evaluate information-mapping capacity, we quantified the network's ability to differentiate and generalize sequential inputs across parameter space. Regions of maximal mapping efficiency coincided with the iterative stability regime of an analytically determined equation governing this glider's dynamics, suggesting a functional link between glider dynamics and information encoding. These results indicate that gliders in recurrent neural networks—shaped by topology, transition function, and parametric configuration—may facilitate general-purpose information processing, with implications for understanding how cortical dynamics support computation.

Disclosures: M. Belluscio: None. **S. Pajevic:** None. **D. Plenz:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

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Program #/Poster #: PSTR292.11/LL71

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

Support: R01-MH-127566
RF1-NS-128974

Title: A Multilevel Theory of Constructive Neural and Decision Variability

Authors: *Z. WANG[1], J. I. GOLD[2];
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Abstract: Variability is an inherent feature of both neural activity and behavior. Increasing evidence suggests that variability is not merely destructive noise that limits performance but rather plays constructive roles. For example, neural variability may support probabilistic reasoning through sampling, while behavioral variability can promote exploration during learning. However, the causes of constructive behavioral variability, the mechanisms of constructive neural variability, and their relation are not well understood. This work aims to develop a multilevel theoretical framework that links decision variability to neural variability. At the behavioral level, we model decision-making as a constrained Markov decision process, in which environmental or internal constraints, such as energetic or informational costs, lead to stochastic optimal policies. In this framework, decision variability arises from sampling of actions from an optimal random distribution shaped by those constraints. We propose that this sampling-based decision variability corresponds to randomness observed in neural activity, providing a principled link between behavioral and neural variability. To study the neural mechanisms underlying this link, we develop circuit-level stochastic networks. We first construct a minimal motif of four Poisson neurons that implement Gibbs sampling to generate a one-dimensional normal distribution. We then build stochastic networks composed of multiple motifs that can sample from multidimensional normal distributions with tunable mean and covariance. Within these networks, the sampling-based neural variability corresponds to the sampling of decision variables underlying decision variability. In addition, we show that top-down signals associated with constraints modulate neural variability by reshaping the covariance structure of the network through gain modulation, ultimately adjusting decision variability for optimal performance. Together, these behavioral-level and circuit-level models provide a coherent mechanism whereby control of neural variability affects decision variability due to constraints. This framework generates testable predictions about how top-down signals, like neuromodulators, may regulate the relationship between neural variability and decision variability in decision-making tasks.

Disclosures: Z. Wang: None. **J.I. Gold:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.12/LL72

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

Title: A Normative Account of Experience and Time-Dependent Representational Drift in Hippocampal Place Cells

Authors: *A. BEHERA, Y. TU;
Ctr. for Computat. Neurosci., Flatiron Inst., New York City, NY

Abstract: Representational drift is observed throughout the neural hierarchy, from early sensory areas such as the visual cortex and olfactory bulb to higher-order memory systems such as the entorhinal-hippocampal complex. While the formation of grid and place cells in novel environments is well characterized, the mechanisms underlying their ongoing drift in familiar environments remain poorly understood. Here, we model hippocampal place field formation through a normative information bottleneck framework grounded in geometric principles. By maximizing spatial predictability while enforcing population sparsity via lateral inhibition, we derive biologically plausible, local learning rules for grid-to-place cell synapses. Because synaptic weight dynamics are largely inaccessible experimentally, we analyze the network's behavior directly in representational space. We propose that representational drift is not random degradation but a signature of the network continually exploring a near-degenerate solution in the loss landscape. Furthermore, our model explains recent empirical findings showing that active experience drives shifts in place field locations, whereas the passage of time primarily modulates firing rates. We show that experience-driven synaptic updates induce spatial diffusion along this attractor, offering a unified account of experience and time-dependent drift.

Disclosures: A. Behera: None. **Y. Tu:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.13/LL73

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

Support: NIMH R00MH125021

Title: Scale-Invariance in EEG: Effort Pushes the Brain Off-Critical, Starting Near Criticality Supports Flexible Choice

Authors: *L. LIM[1], A. BHARDWAJ[4], A.-E. AVRAMIEA[5], K. LINKENKAER-HANSEN[6], A. MITSUTO[2], W. L. SHEW[7], A. WESTBROOK[3], L. TRAN[8];
[2]Dept. of Psychiatry, [3]Psychiatry, [1]Rutgers Univ., Piscataway, NJ; [4]Psychiatry, Rutgers University, New Brunswick, NJ, Piscataway, NJ; [5]Integrative Neurophysiol., VU Univ. Amsterdam, Amsterdam, Netherlands; [6]Vrije Univ., Amsterdam, Netherlands; [7]Physics, Univ. of Arkansas, Fayetteville, AR; [8]Worcester, MA.

Abstract: According to the criticality hypothesis, the brain supports adaptive cognition by operating near a critical point between ordered and disordered dynamics, balancing excessive

stability against unconstrained flexibility. Building on this, we test whether moment-to-moment deviations from criticality (d_2), adapted from the temporal renormalization group theory, index cognitive effort under changing task demands and support adaptive control. Validated with neural mass model simulations, d_2 is minimized when network connections in oscillatory systems balance excitation and inhibition. We then apply d_2 to EEG recorded during task-switching, categorizing trials as Regular or non-Regular. Following stimulus onset, non-Regular trials exhibit elevated d_2 relative to Regular trials, indicating systematic departures from scale invariance and brain criticality as cognitive demands increase. Baseline and task-evoked d_2 jointly predict behavior: lower pre-stimulus d_2 is associated with higher accuracy, faster responses, and a greater propensity to voluntarily switch, consistent with a near-critical state that facilitates readiness and flexible decision-making. Region-specific modulations of d_2 further dissociate frontal midline and posterior dynamics, suggesting that optimal performance depends on a coordinated, spatially structured adjustment around criticality. These findings support the view that the brain does not operate at a fixed critical point. Cognitive effort corresponds to transient, region-specific deviations from criticality that meet momentary task demands, positioning d_2 as a sensitive marker linking scale-invariant EEG dynamics to effort allocation and adaptive cognitive control.

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Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.14/Web Only

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

Support: Chinese Institute for Brain Research

Title: A Phasic-Inspired Artificial Neuron Model for Dynamic Sensory Encoding Using Volatile VO_2 Memristors

Authors: *J. QIU[1], Q. DING[2], Y. YANG[3,4,5,6];
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Abstract: Dynamic changes in sensory inputs carry important information for biological neural systems. Phasic neurons in sensory pathways are specialized for detecting transient changes in

stimuli, while largely ignoring persistent inputs. This response property allows biological circuits to encode temporal information with sparse and event-driven activity. In contrast, many artificial neurons used in neuromorphic systems exhibit tonic-like firing patterns, producing continuous spike trains even when the input remains unchanged. Such sustained activity can lead to redundant spike generation and inefficient representation of dynamic signals.Here, we present a phasic-inspired artificial neuron model based on the volatile switching dynamics of vanadium dioxide (VO_2) memristor. The model combines a capacitor-based voltage isolation mechanism with two coupled leaky integrate-and-fire (LIF)-like pathways to transform analog inputs into spike responses associated with stimulus transitions. Instead of encoding the absolute value of the input, the neuron responds selectively to changes in stimulus intensity.The two pathways generate complementary spike outputs in response to increasing and decreasing inputs. Positive spikes encode the rising phase of the stimulus, reflecting both the magnitude and rate of increase, whereas negative spikes represent the falling phase. In addition, interactions between the two pathways introduce a history-dependent modulation of neuronal responses. When stimulus changes occur consecutively in the same direction, previous firing activity enhances the following response. When an increasing stimulus is followed by a decreasing stimulus, the preceding activity suppresses the subsequent response.Unlike conventional tonic-like artificial neurons that continuously fire under constant stimulation, the proposed phasic-like coding mechanism captures key features of temporal sensory processing and provides a computational model for studying dynamic stimulus representation in neuromorphic neural systems.

Disclosures: J. Qiu: None. **Q. Ding:** None. **Y. yang:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.15/LL74

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

Title: Mechanisms of Timescale Learning in Recurrent Neural Networks

Authors: *F. ACOSTA, A. BERTICS, F. DINC, N. MIOLANE;
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Abstract: Recent studies highlight the role of timescale heterogeneity across both biological brains and artificial neural networks. Recurrent neural networks (RNNs) trained on cognitive tasks are widely used as mechanistic models of neural computation, yet what counts as a “timescale” in an RNN remains ambiguous: per-neuron time-constants τ_i, single-neuron autocorrelations, and emergent network-level timescales are routinely conflated. In this work we show that in linear RNNs, there is a clear correspondence between network-level timescales and task-relevant timescales, an idea we refer to as the \emph{timescale-matching hypothesis}. We test this perspective on heterogeneous variants of two canonical computational neuroscience tasks, the n-bit flip-flop and sine-wave generation tasks, for which task timescales can be

defined based on the temporal structure of the inputs and targets. Trained linear RNNs approximately solve both tasks via sparse, one-to-one matching between select eigenmode timescales and task timescales: decay timescales for the flip-flop, oscillation periods for sine-wave generation. This structure is invisible at the level of individual neurons. Building on this perspective, we show that a power-law initialization of τ_i accelerates learning on heterogeneous tasks for both linear RNNs and nonlinear RNNs. We show that this initialization induces a spectral inductive bias that expands the range of timescales available to the network at the start of learning. Together, these results define, test, and confirm the timescale matching hypothesis and provide mechanistic grounding for heterogeneity of timescales empirically observed in biological neural networks.

Disclosures: F. Acosta: None. **A. Bertics:** None. **F. Dinc:** None. **N. Miolane:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.16/LL75

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

Support: CV Starr Fellowship
P50MH132642
RO1 EY017699
R01 MH137624

Title: Computational role of ephaptic coupling in spiking networks

Authors: *K. BANAIE BOROUJENI[1], S. KASTNER[2];
[2]Princeton Neurosci. Inst., [1]Princeton Univ., Princeton, NJ

Abstract: Neurons share an extracellular medium, so every transmembrane current creates a local field that feeds back onto the membrane potential of nearby cells. This instantaneous effect of the field on neural activity is referred to as ephaptic coupling (EC). EC has been reported empirically at the synaptic, cellular, and network levels, where weak fields shift spike timing and entrain population rhythms. However, whether it serves a computational function remains unclear and is difficult to test, since the field is generated by the same neurons one would need to silence.

Rather than asking whether EC exists, we asked what computational benefit it could provide if present. We built spiking leaky integrate-and-fire (LIF) networks and an ephaptic version (eLIF) that adds a local weighted average of each neuron's neighbors' membrane potentials to its drive. All other features were identical: inputs, tuning, noise, and connectivity. Because coupling raises firing rate on its own, a rate-matched control held spike count equal across models, isolating the field effect from rate.

We used two population tasks. In a ten-stimulus decoding task, all excitatory neurons were

broadly tuned, so identity had to be read from the whole population, not single cells. Each trial mixed a common drive, private noise, and a small stimulus-dependent modulation, creating a distributed, noise-limited code. Compared with the standard model, eLIF improved readout accuracy (nearest-centroid, 40% to 62%), lowered noise correlations (0.12 to 0.03), and produced less tangled population trajectories. The second task probed a sparser regime: each of four patterns used a small active subset of neurons, a sparse code common in cortex, across a range of sparsity and noise levels. With identity relying on a few cells, eLIF again helped, raising accuracy from 54% to 67% (chance, 25%), with larger benefits in sparser conditions. These effects were not simply due to more spikes, as the rate-matched network preserved most of the gain.
These results suggest changes in population geometry, where the field lowers correlated trial-to-trial variability between neurons and widens the separation between stimuli, making the code easier to read out. Because it acts through spatial averaging, the coupling likely trades fine single-cell detail for this gain, consistent with a benefit that is limited to distributed codes. EC may thus be a built-in way to raise the signal-to-noise ratio of cortical population codes without added wiring.

Disclosures: K. Banaie Boroujeni: None. **S. Kastner:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.17/LL76

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

Title: Laplace Representations of Semantic Spaces

Authors: *I. M. BRIGHT[1], J. I. CHAPETON[2], K. A. ZAGHLOUL[3];
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Abstract: Neural representations across cognition often take the form of monotonic “ramps” and localized “bumps,” observed in domains including time, space, and evidence accumulation. Theoretical work has proposed that these ramps and bumps can be understood as a neural implementation of the Laplace transform and Inverse Laplace transform respectively. We extend this ramp and bump motif to more general representations, implementing a method for building “rulers” for semantic spaces. In this framework, populations of neurons with a spectrum of ramp rates encode a representation of a latent variable (e.g. position along a semantic axis), while inverse populations produce localized activity analogous to time or place cells. This framework offers a potential account of neural spiking activity in human anterior temporal lobe, including axis coding, burst dynamics, and representational geometry. Taken together, it suggests that in building the cognitive map, the brain may represent what happened using a similar coordinate system to when and where it happened.

Disclosures: I.M. Bright: None. **J.I. Chapeton:** None. **K.A. Zaghloul:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.18/LL77

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

Support: NSERC Discovery Grant program (RGPIN-2022-04162)
NFRF - Exploration program (NFRFE-2023-00568)

Title: Consciousness in a dish: how metrics of integration, criticality, and complexity are altered by embodiment

Authors: *É. SELLAR[1], J. ST JEAN[1], N. ROULEAU[1,2];
[1]Wilfrid Laurier Univ., Waterloo, ON, Canada; [2]The Allen Discovery Ctr. at Tufts Univ., Medford, MA

Abstract: Studies of consciousness have largely remained exclusive to *in vivo* models, which provide only indirect evidence regarding the phenomenological experience of a system. By contrast, *in vitro* minimal cognitive systems (MCS) offer a platform through which the sufficient and necessary conditions for conscious emergence may be elucidated through experimental control of system complexity. MCS seek to reduce cognition to its most fundamental components: neurons and the means to record from and perturb them. However, many *in vitro* models are limited by both a lack of embodiment resulting in spasmodic and poorly structured neural activity and the absence of tools specifically designed to probe objective measures of consciousness.

To address these limitations, we present the development of an MCS paradigm based on the MaxOne high-density microelectrode array (HD-MEA). This provides both a means of modulating conscious development *in vitro* and a computational toolbox for deriving candidate consciousness metrics from neural recordings. Previous work has demonstrated that deafferented neuronal cultures exhibit spontaneous bursting dynamics reminiscent of epileptiform activity, and that such behaviour can be attenuated through structured electrophysiological stimulation. Building upon this, we investigate how altering degrees of environmental structure and predictability can mold neural dynamics toward states associated with potential markers of consciousness.

Our MCS consists of embryonic day 18 dissociated Sprague-Dawley rat cortical neurons cultured on HD-MEAs. Cultures are exposed to two levels of embodiment through HD-MEA stimulation paradigms: spatially and temporally predictable stimulation and unpredictable stimulation. Network activity is assessed using three candidate consciousness metrics: integrated information (Φ), Lempel-Ziv complexity (LZC), and scale-free avalanche dynamics. LZC is calculated from temporally binned and binarized neural activity to quantify the complexity and compressibility of network dynamics. Avalanche analyses characterize the distribution of

activity cascades and evaluate their adherence to scale-free power-law behaviour, a proposed hallmark of critical dynamics. In parallel, we have developed a workflow that converts HD-MEA recordings into datasets compatible with PyPhi, enabling the calculation of integrated information from large-scale neuronal activity.
This paradigm lays the groundwork towards future investigation of consciousness-related dynamics *in vitro*, providing a platform for testing theories of consciousness in minimally embodied neural systems.

Disclosures: É. Sellar: None. **J. St Jean:** None. **N. Rouleau:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

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Howard Hughes Medical Institute (HHMI), Janelia Research Campus

Title: Adversarial attacks and reverse-phi illusions similarly disrupt motion computation in a fly visual system model

Authors: A. GARCIA-DURAN[1], A. RODRIGUEZ GARCIA[2], M. MOLANO-MAZON[3], A. HYAFIL[1], S. RAMASWAMY[2], ***J. K. LAPPALAINEN**[4];
[1]Ctr. de Recerca Matemàtica, Bellaterra, Spain; [2]Newcastle Univ., Newcastle upon Tyne, United Kingdom; [3]Univ. Politècnica de Catalunya, Barcelona, Spain; [4]Allen Inst., Seattle, WA

Abstract: Illusions expose failures in visual perception. Adversarial attacks exploit vulnerabilities in artificial neural networks. Whether an illusion could be to a neural circuit what an adversarial attack is to an artificial neural network is an open question. Would an illusion for a visual neural system provoke the same failure mode as an adversarial attack? Could adversarial attacks be used to predict illusions? We ask whether perceptual illusions and gradient-optimized adversarial perturbations disrupt internal representations similarly in a connectome-constrained model of the fly visual system in a collision-detection task. To test illusions and adversarial perturbations within the model, we built a differentiable 3D looming collision-detection pipeline in which the visual scene, object textures, motion trajectories, network activity, and decoder outputs are linked end-to-end, enabling gradient-based training for the collision task and optimizing object textures with respect to network states and decoded variables. We find that a reverse-phi looming stimulus, as expected, disables collision detection and disrupts the readout of position and velocity from T4 and T5 activity in task-trained models. An adversarial-texture

looming stimulus, optimized to disable collision detection, produces an equivalent disruption in position and velocity readouts. A comparison of T4 and T5 neural responses shows that the two fundamentally different perturbations - a dynamic, temporally structured illusion and a static, spatially optimized texture - produce similar disruptions of neural activity. To test whether failure and neural activity reflect disrupted motion computation rather than texture novelty, we apply counterfactual restoration. We re-optimize an adversarial texture to re-enable collision detection while penalizing deviation from it. The resulting textures remain equally far from the training distribution, yet restore position and velocity decoding, ruling out texture novelty. This suggests that with differentiable connectome-constrained models, adversarial optimization can uncover stimuli that exploit representational patterns similar to those in classical perceptual illusions, thereby helping to probe and reveal computational mechanisms of perceptual failures.

Disclosures: J.K. Lappalainen: None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.20/LL79

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

Support: R01DA060743-01A1

Title: Steering Recurrent Network Dynamics with Neuronal Response Modulation Enables Supervised Learning through Hebbian Plasticity

Authors: *M. HOGAN, K. BOUCHARD;
Helen Wills Neurosci. Inst., UC Berkeley, Berkeley, CA

Abstract: Across species, neural systems must be capable of rapidly reconfiguring their dynamics to support changing computational demands, from selective attention and context-dependent decision-making to the generation of complex spatiotemporal behaviors. Such flexibility implies rapid, task-driven modulation of neural circuit dynamics on timescales that outpace synaptic plasticity, the canonical mechanism of neural learning. Single-neuron excitatory-inhibitory balance provides a candidate mechanism, modulating two fundamental neuronal response properties: multiplicative gain (slope of the activation function) and additive shift (operating point of the activation function). Such modulation rapidly alters neuronal responses without changing synaptic structure. This suggests that neural circuits operate on two distinct timescales: a fast timescale at which gain and shift (G&S) modulation steers network dynamics to achieve immediate task demands, and a slower timescale at which the resulting activity patterns drive lasting synaptic change through local, activity-dependent plasticity rules. To explore this, we developed an RNN model of gain and shift modulation with Hebbian plasticity to perform time-varying function approximation.
The GS-RNN is a reservoir network with fixed recurrent weights in which per-neuron gain and

shift parameters are task-optimized via gradient descent. GS-RNNs successfully perform function approximation across a diverse battery of temporal tasks, achieving accuracy competitive with fully weight-trained networks while requiring only O(N) versus O(N^2) parameters. Spectral analysis of the reservoir reveals that during training, G&S optimization selectively increases power at task-relevant frequencies, with gain increases accounting for the dominant mode of this effect. Specifically, training increased the gain of target-aligned units, amplified their synaptic drive to downstream units and reshaped the reservoir's effective basis. Finally, when supervised G&S optimization co-occurs with unsupervised Hebbian plasticity on output weights, task-relevant structure consolidates into those synaptic connections. Thus, directed changes in neural activity at faster timescales resulted in lasting structural learning at slower timescales through the interaction of these two adaptive processes. These results establish G&S modulation as a computationally powerful and biologically plausible substrate for multi-timescale adaptation in neural circuits, and raise the possibility that feedback control of neural dynamics by other brain areas may be implemented, in part, through targeted G&S modulation.

Disclosures: M. Hogan: None. **K. Bouchard:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.21/LL80

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

Title: RNNs with equivalent attractor landscapes can implement distinct neural algorithms

Authors: *B. KURTKAYA[1], M. HARMANLI[2], P. YUAN[4], Y. YEMEZ[3], F. DINC[5], N. MIOLANE[6];
[1]Electrical and Computer Engin., Univ. of California Santa Barbara, Santa Barbara, CA; [2]Computer Sci. and Engin., Koc Univ., Sariyer, Turkey; [3]Koc Univ., Istanbul, Turkey; [4]Fudan Univ., Shanghai, China; [6]Electrical and Computer Engin., [5]UC Santa Barbara, Santa Barbara, CA

Abstract: Understanding how neural circuits compute is a central shared goal of neuroscience and mechanistic interpretability. In systems neuroscience, reverse-engineering neural computation often means extracting the attractor landscapes underlying observed dynamics. This approach, however, implicitly assumes attractors identify the computation. Here, we show that two RNNs performing a delayed discrimination task with shared attractor landscapes can implement distinct computation strategies. To reveal these algorithms, we implement a strategy called \textit{out-of-support (OOS) probing}, where combinations of task-relevant inputs expose dynamics occluded by standard task operation, and establish three key results. First, two algorithms map to a functional distinction between working and short-term memory, where one strategy commits to decisions immediately while the other retains the cue memory until the end. Second, which strategy a network adopts is determined by its representational capacity, namely

its rank. Third, overly regularized digital twin models can miss algorithmically relevant dynamics despite accurately reproducing observed trajectories. Overall, these findings position OOS probing as a necessary diagnostic for mechanistic studies of neural computation.

Disclosures: B. Kurtkaya: A. Employment/Salary (full or part-time):; University of California Santa Barbara. **M. Harmanli:** None. **P. Yuan:** None. **Y. Yemez:** None. **F. Dinc:** None. **N. Miolane:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.22/LL81

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

Title: Do Large Language Models Have a Metacognitive Axis?

Authors: *S. YOSHIZAWA[1,2], K. MOGI[2,3];
[1]Tokai university / Sony Computer Sci. Labs. (SonyCSL), Tokyo, Japan; [2]Sony Computer Sci. Labs., Shinagawa-Ku, Japan; [3]The Univ. of Tokyo, Tokyo, Japan

Abstract: Metacognition is increasingly regarded as a necessary capability for advanced AI systems, because reliable agents must not only solve tasks but also monitor the limits of their own knowledge and reasoning (Johnson et al., 2026; Burnell et al., 2026). Current LLMs appear limited in this respect. Dunning-Kruger-like overconfidence has been reported in reasoning and coding tasks, especially in domains where models perform poorly (Singh et al., 2025; Ghosh and Panday, 2026). Yoshizawa et al. (2026) showed that GPT-4's confidence judgements are condition-specific, overconfident, and weakly coupled to task performance compared with humans, suggesting a dissociation between task-level competence and metacognitive monitoring. Related studies argue that hallucinations may arise as confident errors because models cannot fully discriminate truth from error (Yona et al., 2026), and that self-reported confidence can dissociate from token-distribution-based confidence (Bentegeac et al., 2025). Confidence and performance may also be geometrically decoupled inside LLMs, with scaling alone failing to guarantee better calibration (Sanyal et al., 2025). Recent mechanistic studies suggest that LLMs may nevertheless possess limited introspective access to internal states. Lindsey (2025) showed that some models can detect injected concept vectors in their activations, while Macar et al. (2026) investigated the mechanisms of this introspective awareness in open-weight models. Building on these findings, we test whether GPT-2 small, Pythia, Gemma 2B, and Llama 3.2 1B/3B contain a candidate "metacognitive axis" in activation space. We construct steering vectors from confidence- and uncertainty-related contrasts and examine whether they causally modulate reported confidence, abstention, calibration, and confidence-accuracy coupling across task formats. We also discuss whether an "uncertainty gate" exists: an internal mechanism that regulates when uncertainty-related representations become accessible to self-report or behavioral control.

Disclosures: S. Yoshizawa: None. **K. Mogi:** None.

Poster

PSTR292: Principles of Neural Computation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR292.24/LL83

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

Title: Persona Trajectory across Multi-Turn LLM Dyadic Conversations

Authors: *K. INOUE[1], Y. TAMORI[2], S. YOSHIZAWA[3,4], K. MOGI[4,2];
[1]Yokohama Natl. Univ., Yokohama City/Kanagawa Prefecture, Japan; [2]Grad. Sch. of Arts & Sci., The Univ. of Tokyo, Meguro-ku, Japan; [3]Physics, Tokai university, Hiratsuka, Japan; [4]Sony Computer Sci. Labs., Shinagawa-Ku, Japan

Abstract: As Large Language Models (LLMs) become increasingly integrated into human activities, users often interact with them as if they were cognitive agents with a kind of "personality". In response to that, researchers suggested LLMs are role-playing and select among learned "personas" (Shanahan et al.,2023; Marks et al.,2026). Some users personally assign their desirable personas to them, which may appear inconsistent over long interactions. This phenomenon has been variously termed "persona drift" (Li et al.,2024)," identity drift" (Choi et al.,2025) or" agent drift" (Rath 2026) referring to the decay of identity and behavioral consistency in extended conversations. For example, LLM's persona may drift away from the assigned assistant role toward other role-playing and generate unintended outputs. Researchers addressed these problems and proposed technical countermeasures (e.g. steering-based stabilization: Lu et al.,2026), while the problem remains. Here we analyzed how personas drift when two LLM agents engage in multi-turn dyadic conversation from the perspective of mechanistic interpretability. In human personality description, Big Five personality model (John & Srivastava, 1999) is used as a valid measure, which is based on psychometric parameters of openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. In LLMs, "persona vector" (Chen et al.,2025) can directly monitor and control their character traits. We extracted persona vector corresponding to the Big five factors from open-source LLMs, using contrastive activation analysis, and traced their trajectories turn by turn across the conversation. Through these experiments, we investigated (1) whether persona vector trajectories diverge symmetrically or asymmetrically between the two agents, and (2) how these dynamics compare to patterns observed in human dyadic conversation research. Finally, we discuss the implications of observed drift tendencies and representational constraints for LLM alignment, considering cognitive processes related to the neural correlates of Big Five personality (DeYoung et al., 2010). This study would contribute to governing groups of interacting AI agents and understanding differences in interactions between humans and LLMs.

Disclosures: K. Inoue: None. **Y. Tamori:** None. **S. Yoshizawa:** None. **K. Mogi:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.01/LL84

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

Support: Nancy Lurie Marks Family Foundation
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Title: Longitudinal tracking of treatment targets and measures of treatment efficacy for autism spectrum disorders in the context of coupled dyadic interactions during the Anat Baniel Method Neuromovement Intervention

Authors: *E. B. TORRES[1], A. BANIEL[2];
[1]Rutgers Univ. Dept. of Psychology, Piscataway, NJ; [2]Anat Baniel Method Fndn., Greenbrae, CA

Abstract: Autism Spectrum Disorders is fundamentally a motor disorder with underlying multifaceted and tractable causal factors, from genes to complex social interactions (Torres et al. 2013A). Mounting peer-reviewed scientific evidence shows profound differences in cardiac, smooth, and striate muscles suggesting causal links to the motor issues (e.g., Torres, 2021). One less explored aspect of these dysfunctions is the sensation of the returning afferent stream created by self-generated movements (a proxy of the brain's kinesthetic reafference) under such neuromotor developmental differences. Our group has revealed the ubiquitous presence of excessively random motor noise across the broad heterogeneous autism spectrum and characterized it across the lifespan (Torres et al 2013A) with specificity to autism, relative to other nervous systems disorders, under the Precision Medicine framework (Torres et al 2016). A stochastic rule and a scaling power law of motor control maturation inversely relates the excessive noise with excessive randomness, along with the notion of agentic learning (Vaskevich and Torres, 2022). We used spontaneous motions, as they have more plasticity than intentional ones in autism (Torres et al 2013) and can dampen the noise creating the grounds for predictive motor control. Despite these research advances in laboratory settings, very few therapies address the differences in kinesthetic reafference.In this work, we use our Lab-in-a-Box protocol (Elsayed et al., 2021) and tracked three cases of ASD (a 6-year-old female and 2 males, 6 and 12 years old) over 4 months, integrating digital biometrics with parental and teachers' interviews, in the context of the Anat Baniel Method Neuromovement (ABMNM) intervention at a school setting. We digitized the coupled dyadic interactions between the student (child with a diagnosis of ASD) and the practitioner, using 12 APDM Opal sensors (Clario, 128Hz). This intervention is offered 5 consecutive days of 2 sessions a day (AM and PM) followed by monthly sessions (AM and PM). The longitudinal tracking of coupled dyadic motor adaptation, transfer and generalization of various aspects of motor control and coordination was possible by integrating

personalized and standardized micro-movement spikes and stochastic analysis with peripheral network connectivity analyses. We offer clinically informed digital biometrics capturing learning outcomes at different time scales spanning from sub-second to monthly latencies and using rubrics that involve the Nine Essentials defined by (Baniel, 2012; Baniel et al., 2025). We consistently correlated digital biometrics with novel desirable functional outcomes.

Disclosures: E.B. Torres: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CEO of Neurodiversa LLC, Neurodiversa LLC, Rutgers University startup company. **A. Baniel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anat Baniel Method NeuroMovement are registered trademarks, Anat Baniel Method Foundation.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

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Program #/Poster #: PSTR293.02/LL85

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

Support: R01MH134004
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R01AG057892
S10OD032285

Title: ENIGMA-Tractometry Toolbox with multi-level tractography quality control reveals along-tract age associations

Authors: *J. D. ALIBRANDO[1], I. BA GARI[1], T. M. NIR[1], Y. FENG[1], B. CHANDIO[2], F.-C. YEH[3], A. CABALINAN[1], J. VILLALON REINA[1], L. NABULSI[1], C. CHING[1], P. M. THOMPSON[1], N. JAHANSHAD[1];
[1]Imaging Genet. Center, Mark and Mary Stevens Neuroimaging and Informatics Inst., USC, Marina Del Rey, CA; [2]Chem. and Biomed. Engin., West Virginia Univ., Morgantown, WV; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Problem Statement
The ENIGMA Tractometry Toolbox standardizes subject-specific tractography, tractometry, along-bundle analysis, and quality control (QC), using diffusion MRI to map white matter (WM) microstructure along key connections. Tractograms are prone to errors that are difficult to capture with outlier detection alone, so efficient visualization is needed. We present a multi-level ENIGMA QC toolbox for detecting outliers and failures in WM bundles.

Methods

We analyzed 635 Cam-CAN[1] participants (age 18 - 88 yrs) and quantified 63 WM bundles, generated by the ENIGMA pipeline with DSI-Studio[2]. At the cohort level, we computed probability density maps with 1st-99th percentile thresholds to flag cohort-level outliers (Fig. 1B). At the subject level, registration quality was evaluated by overlaying anisotropy maps with HCP-MMP labels (Fig. 1A), and individual bundles were visually reviewed.

HTML pages enabled rapid visualization and rating of outputs (Fig. 1C). We flagged outlier bundles for visual QC using Dice scores and Spearman correlations relative to the ENIGMA atlas[3]. Finally, we assessed associations between age and fractional anisotropy (FA) using along-tract methods, Medial Tractography Analysis[4] (MeTA) and BUndle ANalytics[5] (BUAN), adjusting for sex, age-by-sex, and age-squared. We mapped statistical results using Diffusion Visualization and Explorer (DiVE).

Results

Out of the 63 bundles per subject, 39,419 generated. Flagging Dice score and Spearman correlation outliers reduced the visual QC load to 3,028 tractograms. About 1% of all tractograms failed due to deviations from the group mean or atlas, and were judged biologically implausible. MeTA and BUAN revealed significantly lower FA across all 63 bundles with age (Fig. 1D)($P_{FDR} < 0.05$).

Conclusion

Our QC toolbox, combining bundle metrics, cohort- and subject-level visualizations for streamline quality assurance, reduces the time required for visual QC and may improve reliability of large-scale WM association studies.

[1]Shafto 2014; [2]Yeh 2025; [3]Ba Gari 2026; [4]Ba Gari 2024; [5]Chandio 2020

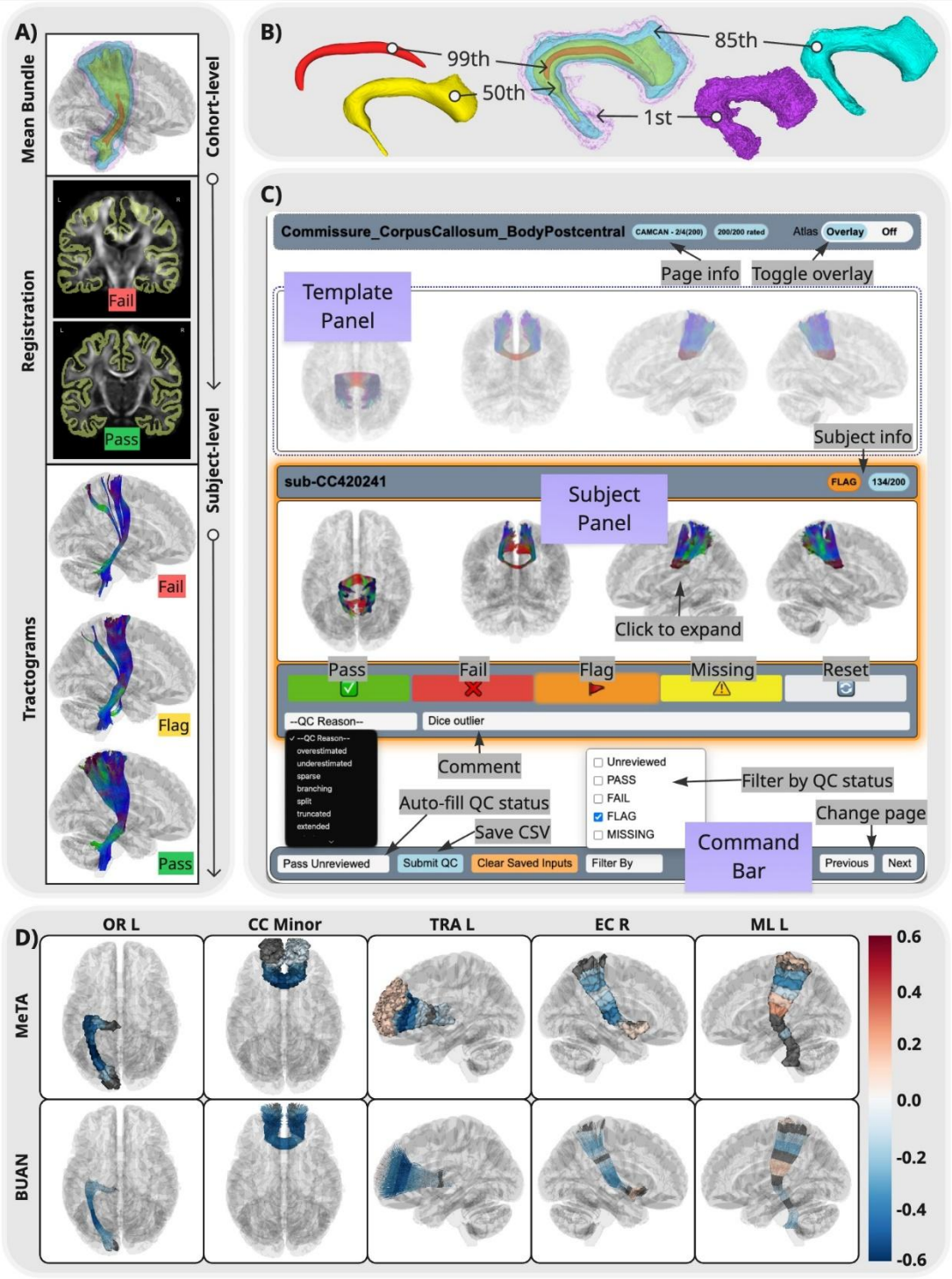


Figure 1. A) Quality control workflow moving from registration, to group, to subject-level visual evaluation. **B)** Iso-surfaces of a mean density map thresholded at four percentiles. **C)** HTML page displaying an automatically flagged Dice outlier and demonstrating page parts and functionality. **D)** Partial effect for age association for BUAN and MeTA for Left Optic Radiation (OR L), Forceps Minor (CC Minor), Left Anterior Thalamic Radiation (TRA L), Right Extreme Capsule (EC R), Left Medial Lemniscus (ML L). Significant non-linear effects were also found in segments of these bundles.

Disclosures: J.D. Alibrando: None. **I. Ba Gari:** None. **T.M. Nir:** None. **Y. Feng:** None. **B. Chandio:** None. **F. Yeh:** None. **A. Cabalinan:** None. **J. Villalon Reina:** None. **L. Nabulsi:** None. **C. Ching:** None. **P.M. Thompson:** None. **N. Jahanshad:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.03/LL86

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

Support: The Beckwith Institute
Clinical Transformation Award
UPMC Rehabilitation Institute

Title: Impact of Online Signal Conditioning and Artifact Removal on Auditory Oddball BCI Performance in Disorders of Consciousness Patients

Authors: *S. SIEGHARTSLEITNER[1,2], J. GRUENWALD[1], A. LIETO[3], A. K. WAGNER[4], K. HILL[5], R. ORTNER[1], K. MAYR[1], C. GUGER[1];
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Abstract: Disorders of consciousness (DoC) present a significant clinical challenge, as patients may retain residual awareness undetectable through standard motor-based behavioral assessments. Brain-computer interfaces (BCIs) have emerged as a valuable modality, probing cognitive function through neural signals independent of motor output. The auditory oddball task is particularly well-suited to this end, eliciting event-related potentials (ERPs) such as the mismatch negativity and P300 reflecting higher-order attentional processing, without requiring intact motor or sensory function as is the case with, for example, vibro-tactile paradigms. Differences in evoked responses between standard and deviant stimuli may thus provide valuable insights, though within- and between-subject variability make objective classification of target (deviant) versus standard responses essential. Patient recordings can be complicated by involuntary movements and muscle artifacts, which may directly compromise signal and classification quality. To address this, the OSCAR (Online Signal Conditioning and Artifact Removal) algorithm was applied as a preprocessing step prior to classification. OSCAR processes EEG data first through frequency decomposition into narrow bands and spatial-temporal whitening to isolate noise components, followed by artifact identification and elimination and signal reconstruction, to yield continuous clean EEG data. Critically, OSCAR operates in a strictly causal fashion, allowing for real-time application. Fifteen recording sessions from 10 patients patients (8 with DoC; one control, one with locked-in syndrome), aged 18 to 64 years and 0.7 to 10.2 years post-injury, were obtained using an auditory oddball BCI (mindBEAGLE, g.tec) paired with a wireless EEG cap and insert earphones. Data were preprocessed using OSCAR and compared to standard preprocessing (notch- and bandpass filtering). Across sessions, OSCAR increased classification accuracy by a median of 7.6%

(interquartile range [IQR]: -0.9 - 14.7%), with raw classification accuracy of 54.6% (IQR: 39.9 - 76.5%) versus OSCAR-preprocessed accuracy of 66.2% (IQR: 52.4 - 88.6%). Performance improved or remained stable in 93.3% of recordings (53.3% improved, 40.0% equivalent, 6.7% declined; ±5% equivalence margin). Universal improvement is not expected, as some recordings were of sufficient signal quality. However, these findings suggest that real-time artifact removal can meaningfully enhance the reliability of BCI-based consciousness assessment in a real-world clinical setting.

Disclosures: S. Sieghartsleitner: A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **J. Gruenwald:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **A. Lieto:** None. **A.K. Wagner:** None. **K. Hill:** None. **R. Ortner:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **K. Mayr:** A. Employment/Salary (full or part-time):; g.tec medical engineering GmbH. **C. Guger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); g.tec medical engineering GmbH.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.04/LL87

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

Support: Rhode Island Foundation Medical Research Grant

Title: Graph Bispectrum Reveals Increased Nonlinear Cortical Coupling During Live Social Interaction in First-Episode Psychosis

Authors: *R. SINGH[1], J. A. NOAH[2], X. ZHANG[2], D. PURUSHOTHAMAN[4], J. HIRSCH[3]; [1]Univ. of Rhode Island, Kingston, RI; [3]Dept. of Psychiatry, [2]Yale Sch. of Med., New Haven, CT; [4]Psychiatry, Yale Univ., New Haven, CT, USA, CT

Abstract: Individuals with schizophrenia experience significant cognitive and social impairments, particularly in understanding and responding to social cues during face-to-face interactions. However, the large-scale brain dynamics underlying these deficits remain poorly understood. We investigated cortical network activity in first-episode psychosis (FEP) using functional near-infrared spectroscopy (fNIRS) recorded during a live face-to-face social interaction paradigm. Participants viewed the face of a live partner whose facial expressions were influenced by emotionally evocative movie clips that were not visible to the participant. To characterize brain network dynamics, we represented fNIRS activity as signals on a cortical network and applied graph bispectrum analysis, our recent method designed to quantify nonlinear interactions among distributed brain activity patterns. We compared these measures between FEP patients and typically developing individuals (14 FEP subjects and 18 typical

controls). Conventional graph spectral power measures were broadly similar between the two groups, indicating comparable overall distributions of cortical activity. In contrast, measures of nonlinear network interactions were consistently elevated in the FEP group. Specifically, graph bicoherence revealed stronger nonlinear coupling across multiple cortical network modes, and normalized graph bispectral energy was increased in FEP relative to controls ($p = 0.0507$). These findings suggest that psychosis is associated with altered nonlinear coordination of distributed cortical networks during live social interaction.
Our findings complement our previous work demonstrating that multimodal neural representations derived from live social interactions can distinguish FEP from typically developing individuals and predict symptom severity (Singh et al., Frontiers in Psychiatry, 2025). Our results demonstrate that nonlinear network measures provide information beyond conventional graph spectral analyses and may reveal aspects of social brain dysfunction that are not captured by traditional connectivity approaches. Graph bispectrum provides an interpretable measure of nonlinear cortical network interactions. These nonlinear graph features may serve as candidate biomarkers for early psychosis and motivate the development of future interpretable graph neural network architectures that explicitly model nonlinear brain network interactions for FEP classification and biomarker discovery.

Disclosures: R. Singh: None. **J.A. Noah:** None. **X. Zhang:** None. **D. Purushothaman:** None. **J. Hirsch:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.05/LL88

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

Support: Rhode Island Foundation

Title: Interpretable Spatiotemporal Graph Neural Networks for Classification and Biomarker Identification of ADHD in Children

Authors: *S. VEERA[1], M. LIM[1], A. LEVINSON[2], J. GAUDREAU[1], A. BARON[3], V. HARWOOD[3], R. SINGH[4], N. LOGAN[5];
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[3]Communicative Disorders, [4]Electrical Computer and Biomed. Engin., [5]Kinesiology, Univ. of Rhode Island, Kingston, RI

Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder in children, characterized by inattention and hyperactivity/impulsivity. However, objective biomarkers that can differentiate children with ADHD from neurotypical (NT) children are still limited. Resting-state electroencephalography (rs-EEG) provides a non-invasive method

for measuring baseline brain activity and may capture signals for identifying these differences. Because rs-EEG signals exhibit complex spatial dependencies across electrodes and temporal dynamics over time, this study aims to develop and evaluate a spatiotemporal machine-learning framework based on a Graph Convolutional Network-Long Short-Term Memory (GCN-LSTM) model to distinguish between individuals with ADHD from NT children using rs-EEG. Resting state EEG data and demographic information were collected from 79 children aged 10.43 ± 2.80 years (53% female(N = 48); 37% ADHD(N = 29)). These signals were preprocessed and divided into 5-second windows, where they would then be fed into the GCN-LSTM model. The model consisted of a structural connectivity graph that directly mapped graph nodes to the locations of 128 EEG electrodes placed on the scalp of the participants during recordings. The edges of the graph were determined via a distance threshold between the electrode locations. To improve interpretability and identify relevant brain regions contributing to ADHD classification, learnable attention coefficients were assigned to nodes prior to the classification layer. This model achieved an overall accuracy of 97.7% and an F1 score of 0.9817. Notably, the classification performance across age groups did not change significantly, with accuracies ranging from 95.4% among ages 11.7-13.6 years to 99.3% among children aged 10-11.7 years. These findings suggest that rs-EEG combined with machine learning may distinguish children with ADHD from NT, regardless of age. Visualizations based on learned attention coefficients were also created for ADHD and NT participants, enabling biomarker identification for ADHD in children. Together, these approaches may offer a promising step toward developing more objective data-driven tools to support ADHD assessment.

Disclosures: S. Veera: None. **M. Lim:** None. **A. Levinson:** None. **J. Gaudreau:** None. **A. Baron:** None. **V. Harwood:** None. **R. Singh:** None. **N. Logan:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.06/LL89

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

Support: AIMAHEAD

Title: AN INTERPRETABLE MACHINE LEARNING FRAMEWORK FOR SMALL CLINICAL COHORTS: LESSONS FROM ALL OFUSANALYSIS OF HIV AND SUBSTANCE USE DISORDER COMORBIDITY

Authors: *D. ACHEAMPONG[1], A. NKWAIN[1], M. C. GONDRÉ-LEWIS[2];
[2]Anat., [1]Howard Univ. Col. of Med., Washington, DC

Abstract: Applying machine learning (ML) to small, imbalanced clinical populations and scientific datasets, remains a persistent challenge. Comorbid HIV and substance use disorder

(HIV+SUD) is , a neurobehaviorally important population that shares social, behavioral, and health -burden profiles with HIV- and SUD-only groups. We developed an interpretable ML framework to test how cohort design, imbalance handling, and preprocessing impact HIV/SUD classification using NIH's All of Us dataset. Control, HIV-only, SUD-only, and HIV+SUD groups' health status were verified at recruitment. We constructed sequential datasets: strictly matched, moderately expanded, larger imbalanced, and an ancestry-matched balanced set after removal of genetic data restrictions to increase HIV+SUD participant numbers. Survey predictors spanned demographics, socioeconomic status, housing, education, employment, alcohol and tobacco use, recent substance-use indicators, disability, and overall health. Responses were cleaned, deduplicated, and encoded using binary, ordinal, one-hot, or numeric mappings, with feature-specific missingness rules that separated true NaNs from refusal, uncertainty, and skip responses. We compared multinomial logistic regression, Random Forest (RF), Balanced RF, SMOTE and RandomOverSampler (ROS) methods, LASSO-CV, XGBoost, and unsupervised K-Means clustering. Most supervised models learned separable patterns for Control, HIV, and SUD participants but failed to classify the smallest HIV+SUD comorbid group. Strict matching produced balanced but small classes (117 per class; RF accuracy=0.553; F1 for HIV+SUD = 0.522). Moderate expansion of the dataset raised accuracy to 0.577 but yielded HIV+SUD F1=0.000. A larger imbalanced set with ROS reached RF accuracy=0.731 but produced HIV+SUD F1=0.000, demonstrating that additional data and oversampling alone were insufficient to increase F1. Removing genetic restrictions increased the HIV+SUD participants from 117 to 558. In the final balanced set (558/class), The F1 score dramatically increased to 0.5093, with accuracy of 0.568 achieving better discrimination from SUD- or HIV-only groups. LASSO-CV achieved slightly better performance (accuracy=0.577, F1=0.514). HIV+SUD one-vs-rest AUC reached 0.835 under LASSO-CV. Persistent SUD and HIV+SUD mis-classification and K-Means overlap indicate shared SDOH, behavioral, and health-burden profiles. By prioritizing cohort design, imbalance correction, and minority-focused evaluation over accuracy alone, this framework offers generalizability for extracting reliable signal from clinical and scientific populations.

Disclosures: D. Acheampong: None. **A. Nkwain:** None. **M.C. Gondré-Lewis:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.07/LL90

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

Title: Personalized Profiling of Efficacy in Neuromotor Development Using the Feldenkrais Method: Towards Digital Accounts of Awareness Through Movement

Authors: *T. BERMPERIDIS[1], E. B. TORRES[4,2,3];
[2]Ctr. for Cognitive Sci., [3]Computat. Biomedicine Imaging and Modelling, Computer Sci. Dept.,

[1]Rutgers Univ., Piscataway, NJ; [4]Psychology Dept, Rutgers Univ. Dept. of Psychology, Piscataway, NJ

Abstract: Cerebral Palsy (CP) is often difficult to detect by observation alone. Early detection would help families choose therapies to help develop motor fluidity, control, coordination and learning from early infancy. However, there is currently a gap in therapies that serve this purpose in infancy. There is also a shortage of outcomes measures permitting the assessment of therapy effectiveness over time, particularly in therapies that are designed to combine clinical settings with continuation of the therapies (by the parents) at home. In this work, we offer a new platform for highly scalable mobile assessment, to longitudinally track the progress of the outcomes of the Feldenkrais Method (FM) in 5 young infants (up to 5 months old) and 5 young children (3-9 years old) with CP. FM evokes awareness of self-generated bodily motions and enhances patient-clinician interactions. We hypothesize that FM also evokes in the child a quantifiable sense of motor agency (SMA), which we can measure through personalized indexes of motor autonomy and predictive motor control. Therapy took place both at the clinic, with the therapist, and at home, with the parents. Five neurotypical infants were also tracked for 25 weeks, to normative milestones according to Prechtl's General Movement Assessment. Specifically, we evaluated the quality and the transitions of spontaneous movements towards intentional patterns. We integrate skeleton positional data from 3D video pose estimation with a scalable and personalized platform developed in the lab for detecting and characterizing human micromovements, non-linear dynamics and principles of motor control, to develop biometrics that quantify the infant's/child's SMA. We posit that infants and children with CP can achieve normative milestones and a SMA but do so along delayed outcomes. We assessed the effectiveness of the FM by detecting this delayed development along longitudinal trajectories of scalable biometrics. The results showed a noise reduction and restructuring of spontaneous motions in the CP cohort that resembles the trend detected in neurotypicals. This outcome was consistent across distal, medial and proximal body parts. Using novel biometrics, we can detect an increased SMA in infants and children after repeated FM sessions, both in a clinical setting and at home. We also quantified increased synergies and coordination between body parts in CP and neurotypicals alike. This assessment platform requires brief videos (2min) and a sampling frequency of 30 Hz, a promising outcome that lays the foundations for designing easy-to-use, mobile, remote and non-invasive assessment applications to assist clinicians and families.

Disclosures: T. Bermperidis: None. **E.B. Torres:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.08/LL91

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

Support: New Jersey Department of Labor - Innovation and Research Fellowship Program
Nancy Lurie Marks Family Foundation
Sensory Motor Integration Lab

Title: Assessing efficacy and progress of sensory and occupational therapies on nervous system regulation in Autism Spectrum Disorder

Authors: *M. ELSAYED[1,2], E. B. TORRES[3];
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Abstract: Despite years of research across the fields of psychology, biology, and neuroscience, the causes of Autism Spectrum Disorder (ASD) are not clearly understood, leading to a scarcity of targets for treatment. A good target candidate from our motor control research is to reduce the noise-to-signal ratio of a variety of autonomic and voluntary movements' signals. This is with the overarching goal of improving bodily sensations and kinesthetic reafferent feedback, which in turn can improve the balance between autonomic and predictive control signals, the sense of action ownership, and the overall sense of motor agency. While many therapeutic approaches currently exist, there is a gap in our knowledge regarding their purported benefits to autistic individuals and their tracking of elevated noise in the physiological signals registered by biosensors. Most approaches used to evaluate treatment progress and effectiveness often rely on behavioral observation which is inherently subjective and limited. There is also a lack of research regarding how these therapies influence underlying biology to objectively assess improvements in nervous system regulation. In this work we aim to fill the gap by examining how sensory and occupational therapies influence autonomic and peripheral nervous system functioning via wearable sensing technologies and video-based kinematics estimation. We analyze biophysical signals obtained from the heart (via electrocardiography) as well as facial and bodily movements (via video and motion sensors, respectively) before, during, and after therapeutic activities. Leveraging the digital revolution and precision medicine approaches developed in our lab, we can individually track levels of distress/nervous system dysregulation that are elevated or dampened during or after therapeutic activities. We offer streamlined pipelines for stochastic data analysis that reveal changes in autonomic and peripheral nervous system responses clinically relevant to ASD and related neurodevelopmental disorders. Cardiac rhythms alone provide meaningful insight regarding the individual's emotional regulation and behavioral adaptation based on biometrics of sympatho-vagal balance. With our highly scalable, multi-modal, and integrative approach, we can bring our research to the community and begin to paint a more wholistic picture regarding how therapies influence nervous system activity and internal states of regulation, ultimately leading to improvements in tracking treatment progress, efficacy, and the ability to objectively tailor therapeutic interventions in a personalized manner.

Disclosures: M. Elsayed: None. **E.B. Torres:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.09/LL92

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

Title: Modeling 12-Month Aneurysm Prognosis from Hemodynamics: A Biomechanics-Driven Conditional Markov Framework

Authors: *M. LI;
Univ. of Washington, Seattle, WA

Abstract: Rupture of an intracranial aneurysm can cause bleeding in the brain and long-term disability, yet there is no unified framework to translate blood-flow conditions and early post-treatment status into an individualized 12-month recovery outlook. We present an end-to-end probabilistic pipeline that maps aneurysm hemodynamics to rupture risk and subsequently to post-rupture functional outcomes, enabling individualized 12-month recovery forecasting. We construct synthetic patient profiles by sampling within literature-supported boundary values and set-up guidelines for these metrics to model realistic measurement and physiologic variability. For each profile, we estimate day-by-day rupture risk using an established statistical rupture-risk model. To represent post-rupture recovery, we use a Continuous Time Markov Chain (CTMC) in which patients move between functional outcome states, which are calibrated with outcome distributions reported by the International Subarachnoid Aneurysm Trial (ISAT) at 2 and 12 months on the modified Rankin Scale (mRS), a standard measure of functional independence. Coupling rupture risk with recovery transitions produces patient-specific trajectories and quantifies uncertainty from both biomechanical variability and post-rupture recovery. Simulations demonstrate that variations in baseline hemodynamic parameters produce distinct long-term functional outcome profiles, highlighting the prognostic influence of aneurysm hemodynamics beyond rupture risk alone. The goal of this project is to provide a dataset-agnostic framework to help clinicians input baseline post-treatment data and visualize individualized recovery probabilities.

Disclosures: M. Li: None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.10/LL93

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

Support: Nancy Lurie Marks Family Foundation Career Development Award

Title: Multimodal Detection of Stress and Anxiety Using Affective Facial Behavior and Heart Rate Variability: Digital Biomarkers of Human Stress Regulation

Authors: *J. A. RAMOS[1], E. B. TORRES[2];
[1]Rutgers Univ., New Brunswick, NJ; [2]Psychology Dept, Rutgers Univ. Dept. of Psychology, Piscataway, NJ

Abstract: Multimodal Detection of Stress and Anxiety Using Affective Facial Behavior and Heart Rate Variability (HRV): Digital Biomarkers of Human Stress Regulation **Motivation:** Stress and anxiety influence human behavior through dynamic autonomic interactions involving cardiac, cognitive, and affective motor regulation. However, traditional assessments of psychophysiological stress often rely on subjective observations, overlooking rapid, autonomic fluctuations in nervous system activity during cognitive, physical, and emotional state transitions. Furthermore, traditional analyses often assume a single theoretical distribution for population statistics, neglecting individualized nuances in stress-regulation-related activity. Here, we use a personalized approach to ask whether HRV and affective facial behavior can be used to empirically characterize individualized patterns of stress-related changes following performance challenges. **Methods:** 20 participants completed a standardized multimodal assessment protocol comprising a resting baseline measurement, brief facial assay, cognitive assessment, a physical challenge, and post-task recovery evaluation. Continuous cardiac activity (Polar H10 chest strap, 1KHz) signals for HRV analysis and brief facial videos (30Hz) were collected pre- and post-task challenges. OpenFace software estimated facial landmarks, action units, eye activity, and head motions during affective state transitions. HRV analyses included time-domain and frequency-domain metrics associated with sympathetic and parasympathetic regulation. In parallel, IBI-derived and facial micro movement fluctuations were empirically modeled using the continuous Gamma family of probability distributions to track shifts in their stochastic signatures. **Results:** Personalized changes in autonomic and affective behavioral dynamics following performance demands were evident relative to baseline. HRV-derived metrics showed alterations in cardiac regulation consistent with stress-related autonomic state transitions, via shifts in stochastic patterns in response to cognitive and physical demands. Individualized facial micro-movement analyses demonstrated significant changes in affective motor variability across parcellated facial regions, suggesting a proxy probability map of cardiac signals of personalized levels of stress tolerance. **Conclusions:** These findings offer a multimodal digital biomarker framework to monitor individualized stress responses and resilience through combined physiological and behavioral measurements.

Disclosures: J.A. Ramos: None. **E.B. Torres:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.11/LL94

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

Support: Nancy Lurie Marks Family Foundation
O'Sullivan Foundation

Title: Proxy signal of autonomic sympathetic overdrive defines autism subtypes

Authors: *A. E. TIAN[1], J. VERO[2], E. B. TORRES[2,3,4];
[1]Rutgers Univ., New Brunswick, NJ; [2]Psychology, [3]Ctr. for Cognitive Sci., [4]Computat. Biomedicine Imaging and Modelling Ctr., Rutgers Univ., Piscataway, NJ

Abstract: Background: Autism spectrum disorder (ASD) is a broad, heterogeneous condition that encompasses different support needs and speaking abilities. In recent years, research from our lab has detected persistent levels of sympathetic overdrive in nonspeaking ASD. Facial micro-expressions and heart rate variability (HRV) characterizing their autonomic levels of dysregulation showed evidence that the ophthalmic region of the face offers a proxy for erratic HRV. Here we hypothesize that persistent sympathetic overdrive in nonspeaking ASD saturates the autonomic eye signal (pupil dilation), leading to narrower ranges of signal dispersion compared to verbal ASD.Methods: Eye signals (iris, pupil, gaze) were extracted using OpenFace from brief (60 sec) videos during resting, smiling, and surprise-expression conditions in 17 nonspeaking ASD and 29 verbal ASD participants. Using an analytical pipeline developed by our lab, we extracted smooth positional trajectories of eye landmarks (pixels) and temporal speed profiles (pixels per frame at 30 Hz). These peak-valley streams yielded micromovement spikes (MMS), a standardized data type scaling out allometric effects due to anatomical disparities and expressing micro-peak fluctuations away from the empirically derived Gamma distribution mean. Using maximum likelihood estimation and 95% confidence intervals, we derived the Gamma shape-scale profiles best fitting the frequency distribution of MMS peaks and expressed them on a log-log plane. Dispersion was compared with a one-recording-per-person resampling control, plus Brown-Forsythe and generalized variance tests, using permutation and size-matched draws. Further, Delaunay triangulation provided convex-hull areas for comparison between the two unequal-size groups.Results: Nonspeaking ASD scatter was tighter and more homogeneous than verbal ASD scatter in every signal and condition (including iris-pupil area differences as a proxy for pupil dilation; median verbal/nonspeaking dispersion ratio about 1.6-2.5), strongest at rest (Brown-Forsythe p less than 0.05). Both groups shared a common inverse shape-scale power law (R2 greater than 0.97), differing in scatter dispersion along a shared manifold rather than in slope.Conclusions: These preliminary results lend support to our hypothesis of autonomic saturation in persistent sympathetic overdrive, which may result in a narrower range of autonomic regulation in nonspeaking ASD. Ongoing work will test a neurotypical cohort to anchor these distributions to normative ranges and test this metric's value for stratification and longitudinal monitoring.

Disclosures: A.E. Tian: None. **J. Vero:** None. **E.B. Torres:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

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Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.12/LL95

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

Support: Cortex Project

Title: Predicting drug profiles from preclinical pharmaco-EEG: a deep learning approach for CNS drug discovery

Authors: ***M. VILLALBA**[1], D. DARANKOUM[1,2], E. GRONLIER[1], C. ALLIOUX[1], B. CARABALLO[1], C. DUMONT[1], C. HABERMACHER[1], S. GRUDININ[2], J. VOLLE[1]; [1]R&D, SynapCell, Saint-Ismier, France; [2]Lab. Jean Kunztmann, Univ. Grenoble Alpes, CNRS, Grenoble, France

Abstract: Electroencephalography (EEG) is a highly translational technique that provides direct access to brain activity and captures neural oscillations with high temporal resolution. In central nervous system (CNS) drug discovery, EEG is a powerful tool for identifying pharmacodynamic signatures and supporting compound profiling. However, CNS compounds often involve complex mechanisms affecting multiple neural pathways, making therapeutic characterization challenging during early-stage development and highlighting the need for efficient predictive tools. To address these challenges, we developed a large-scale standardized pharmaco-EEG database of neural oscillations recorded in healthy mice. This dataset comprises more than 30 reference compounds spanning five major CNS drug areas: antidepressants, anxiolytics, antipsychotics, antiepileptics, and psychedelics. Healthy mice were used to isolate drug-induced signatures without disease-related confounds. Multi-channel EEG was acquired using standardized electrode placement and protocols to ensure consistency across cohorts and facilitate robust computational analysis. Building on this dataset, we introduce CoSupFormer, a deep neural network architecture designed to learn meaningful patterns from EEG data for pharmacological profile prediction. The model was specifically developed to address key EEG challenges, including noisy channels, multi-frequency dynamics, and overlapping pharmacological properties where compounds may exhibit features of several drug classes. CoSupFormer was evaluated on both unseen subjects and independent compounds. It demonstrated strong performance under challenging settings where previous state-of-the-art approaches showed substantial degradation. On our dataset, CoSupFormer reached an F1-score of 0.71, against 0.53 for the best existing state-of-the-art approach. When applied to previously unseen compounds, it successfully identified lorazepam as anxiolytic-like and olanzapine as antipsychotic-like, demonstrating generalization beyond the training set. These findings suggest that drug-induced EEG dynamics contain discriminative signatures supporting pharmacological class prediction. Together, our pharmaco-EEG dataset and CoSupFormer establish a standardized EEG-based framework for pharmacological characterization and drug profile prediction in CNS drug discovery. By enabling scalable analysis of drug-induced neural signatures and generalizing to unseen compounds, this approach offers a promising decision-support tool for compound prioritization, pharmacological screening, and repurposing strategies.

Disclosures: M. Villalba: A. Employment/Salary (full or part-time):; SynapCell. **D. Darankoum:** A. Employment/Salary (full or part-time):; SynapCell. **E. Gronlier:** A.

Employment/Salary (full or part-time):; SynapCell. **C. Allioux:** A. Employment/Salary (full or part-time):; SynapCell. **B. Caraballo:** A. Employment/Salary (full or part-time):; SynapCell. **C. Dumont:** A. Employment/Salary (full or part-time):; SynapCell. **C. Habermacher:** A. Employment/Salary (full or part-time):; SynapCell. **S. Grudinin:** None. **J. Volle:** A. Employment/Salary (full or part-time):; SynapCell.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.13/LL96

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

Support: Alzheimer's Association, The Michael J. Fox Foundation for Parkinson's Research, and CurePSP Sleep Contributions to Neurodegeneration Grant SCN-25-1470707
ARCS Foundation

Title: Physiological relevance of training data shapes generalization of large-scale models: A multi-disorder transfer-learning study

Authors: *X. A. VELEZ[1], K. RAMEZAN[2], Q. LI[2], D. ANDERSON[1], S. NASIRI[2], Y. KIARASHI[2], G. CLIFFORD[2];
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Abstract: Large-scale pretrained models, often referred to as foundation models, are increasingly used for electroencephalography (EEG) analysis. However, their ability to generalize to downstream EEG-based disorder detection and the impact of training-evaluation data alignment remain unclear. We evaluated nine pretrained models spanning three domains: sleep physiology (SleepFM, SleepTransformer, TinySleepNet), generalized physiology (LaBraM, EEGPT, BIOT), and generalized time-series modeling (TimesFM, Moirai, MOMENT). We hypothesized that learned representations would generalize to downstream neuropsychiatric disorder classification, with performance scaling according to similarity between pretraining and evaluation data. To assess generalization across neurodegenerative and psychiatric conditions, we performed classification of Alzheimer's disease (AD; n=64), frontotemporal dementia (FTD; n=51), schizophrenia (SZ; n=28), and major depressive disorder (MDD; n=53) using three publicly available eyes-closed resting-state EEG datasets. For computational feasibility, embeddings were extracted from constrained five-channel subsets selected to maximize spatial separation across the scalp in a 4-nearest-neighbors exclusion paradigm. Disorder detection performance using support vector machines and eXtreme Gradient Boosting classifiers was compared with standard EEG band-power features. All pretrained models yielded lower AUROC than band-power features across all conditions except MDD,

where one model (MOMENT) performed best. This suggests that the pretrained models did not capture the spectral characteristics most relevant for separating the evaluated datasets. For dementia classification, models pretrained on overnight EEG achieved the strongest performance, indicating that sleep physiology models encode neurodegeneration-related features that are informative even during wakefulness. One possible explanation is that overnight EEG contains extended segments of eyes-closed activity that more closely resemble the evaluation data. Model rankings were negatively correlated between dementia and SZ classification ($\rho = -0.54$, $p = 0.13$) and between dementia and MDD classification ($\rho = -0.67$, $p = 0.05$). These results suggest that representations supporting neurodegenerative disorder detection do not readily generalize to psychiatric disorder classification, and vice versa. Our findings highlight the importance of matching pretraining data and populations to downstream EEG applications and suggest limited generalizability of current large models across neuropsychiatric disorders.

Disclosures: X.A. Velez: None. **K. Ramezan:** None. **Q. Li:** None. **D. Anderson:** None. **S. Nasiri:** None. **Y. Kiarashi:** None. **G. Clifford:** None.

Poster

PSTR293: From Computational Tools for Brain and Behavior to Clinical Prediction and Digital Biomarkers

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR293.14/MM1

Topic: D.03. Stroke

Title: A pulsatile electrical circuit model of the Circle of Willis and Clinical Applications

Authors: *B. R. SHETH[1], N. THOTA[2];
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Abstract: Our goal is to provide and explore a realistic model of blood flow in the Circle of Willis (CoW) in humans and leverage it to pinpoint structural weaknesses in individual arteries of the CoW. The CoW is a circulatory anastomosis of several arteries in the inferior side of the brain supplying oxygenated blood to over 80% of the brain. In an extension of prior work, we have now designed a zeroth-order pulsatile or AC electrical circuit model of the CoW in which individual arteries of the CoW were modeled as resistors in parallel with capacitors to account for flexible arterial walls. A pulsatile cardiac PQRST wave was modeled. The internal carotid artery (ICA) and basilar artery were inlets in our model, and the rest were outlets. Difference in blood pressure along individual arteries was modeled using Poiseuille's Law, with values of diameter and length informed by the literature. Inter-arterial correlations were additionally modeled via a Gaussian copula to capture physiologically realistic co-variation among vessel dimensions. We modeled three common variations in the CoW (A. complete; B. missing right posterior cerebral artery P1 (RPCA1); C. missing right anterior cerebral artery A1 (RACA1)), which together account for nearly 90% of the variation across the human population and for

which clinical flow data are available. The flow (current) solution to each individual model was then computed using numerical solutions to differential equations based on electric circuit theory, then compared with empirical data on blood flow (Zarinkoob et al., 2015). We analyzed further only those models whose current solutions (flow rates) for all arteries in the model fell within empirical range for all three variations (n = 291,990). Analysis identified arteries where the flow exceeded expectations and therefore, higher shear stress and likely sites for aneurysm and/or stroke. Three artery pairs in individual models showed higher than expected flow rates in all variations tested–ICA, middle cerebral artery (MCA) and PCA1 with bilateral asymmetry for the ICA and MCA pairs (LICA > RICA; RMCA > LMCA). PCA1 showed the highest overload (47–96% of models), stable across a wide range of flow rate cut-offs. LPCA1 risk was highest in the variation missing RPCA1 (58–97% of models) and RMCA showed greater risk than LMCA across all three variations. For variation C with the missing RACA1, the risk for its bilateral counterpart LPCA1 was elevated (50–96% of models); LACA1 showed compensatory increase in blood flow. Flow in the models was laminar (median Reynolds numbers in the range 320–576 < 2300, the threshold for intermediate flow), indicating that the risk comes from redistribution, not turbulence.

Disclosures: B.R. Sheth: None. **N. Thota:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.01/MM2

Topic: J.07. Data Analysis and Statistics

Support: UM1MH130981
R01MH060974
F32MH138113

Title: Integrating anatomical and functional MRI, single cell multiomics, and spatial transcriptomics in macaque neocortices across and within individuals

Authors: *B. Q. ROSEN[1], D. HU[2], S. C. SEEMAN[3], F. YAZDANIBANAFSHEDARAGH[2], T. COALSON[1], J. HARWELL[1], M. HUANG[3], A. GARCIA[3], R. D. HODGE[3], T. IKEDA[4], T. HAYASHI[4], H. ZENG[3], E. LEIN[3], D. C. VAN ESSEN[1], W. FREIWALD[2], M. F. GLASSER[1]; [1]Washington Univ. in St. Louis, Saint Louis, MO; [2]Rockefeller Univ., New York, NY; [3]Allen Inst., Seattle, WA; [4]RIKEN Ctr. for Biosystems Dynamics Res., Kobe, Japan

Abstract: The primate cerebral neocortex supports an extraordinary array of complex behaviors, but the spatial organization of cell types and gene expression underpinning these functions is poorly understood. Due to interindividual variability, cellular and molecular features are optimally compared to functional organization in the same individual. A key challenge is to accurately register antemortem anatomical/functional MRI data to postmortem tissue samples

dissected for single-nucleus multiomic analyses or histologically sectioned for spatial transcriptomics (STx), as significant deformation occurs during removal, slabbing, and mounting. These challenges are particularly acute in gyrencephalic primate neocortex due to the large size and complex folding of the neocortical sheet. We present here data from (i) two exquisitely well-characterized macaques with high-quality antemortem anatomical MRI and >40 hours of awake task and resting-state fMRI recordings each, denoised using state-of-the-art HCP-style pipelines, (ii) an integrated pipeline for functionally guided postmortem multiomic tissue sampling and analysis demonstrated in the same individual, and (iii) STOmics Stereo-Seq (Macaque 1) and 10x Xenium (Macaque 2) STx sections precisely registered to the anatomical and functional MRI by aligning T1w contrast to white and gray matter STx features. The demonstrated precise registration to MRI allows multiomic and spatial transcriptomic data to be accurately registered between individuals and to common coordinate frameworks though established techniques developed for MRI. Functional imaging revealed an intriguing interdigitation of novel task-negative default mode network patches with visual category-selective patches in inferotemporal cortex, and functional correlativity between the superior temporal gyrus and the anterior bank of the inferior arcuate sulcus, suggesting a homolog of the human language network. Analysis of STx revealed a diversity of neocortical cell type distributions, including both spatially restricted cell types and cell types with broad heterogeneous spatial distributions. In preliminary analyses, gradients in transcriptomic features enabled delineation of some areal boundaries but were not uniformly consistent with anatomical and functional MRI gradients. Taken together, these findings provide a solid foundation for bridging the gap between the microscale cellular and molecular neuroscience of transcriptomics and mesoscale systems and cognitive neuroscience of brain imaging.

Disclosures: B.Q. Rosen: None. **D. Hu:** None. **S.C. Seeman:** None. **F. YazdaniBanafsheDaragh:** None. **T. Coalson:** None. **J. Harwell:** None. **M. Huang:** None. **A. Garcia:** None. **R.D. Hodge:** None. **T. Ikeda:** None. **T. Hayashi:** None. **H. Zeng:** None. **E. Lein:** None. **D.C. Van Essen:** None. **W. Freiwald:** None. **M.F. Glasser:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.02/MM3

Topic: J.07. Data Analysis and Statistics

Support: NIH/NIA R01 AG092088

Title: Data Driven Decomposition of Precisely Aligned Fiber-Orientation Preserving Probabilistic Tractography Connectomes with Non-Negative Matrix Factorization

Authors: *H. ZHOU[1], T. COALSON[1], B. Q. ROSEN[2], H. RAFIPOORASKESTANI[3], F. LANGE[4], N. YOSHIDA[5], T. HAYASHI[6], S. SOTIROPOULOS[7], S. JBABDI[8], D. C. VAN ESSEN[9], M. F. GLASSER[10];

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Abstract: The Human Connectome Project (HCP) aimed to describe the functional and structural connectivity of the human brain. Although there has been tremendous progress in data-driven decomposition of functional connectivity data, work with HCP probabilistic tractography-based connectomes has been more limited. Initial work using Non-negative Matrix Factorization (NMF) of structural connectivity matrices into white matter tracts and grey matter projection territories was promising; however, it was computed at less than native resolution of the HCP diffusion data, did not use connectivity data that was aligned across individuals using white matter fiber orientations, and did not preserve the fiber orientation of probabilistic streamlines in areas of crossing fibers, due to computational and algorithmic limitations. Recent advances in GPU computing, memory hardware, and software development now enable us to introduce a set of HCP pipelines and algorithmic improvements that address these limitations. We implemented FSL's MultiModal Registration Framework (MMORF) and generated a new HCP group average using T1w, T2w, and diffusion fiber orientations with much more precise alignment of the white matter tracts in OMM-1 space. We have adapted a long-dormant "matrix4" probabilistic tractography connectome storage format (gray matter X white matter X fibers) within FSL's probtrackx from single threaded CPU to the GPU, enabling reasonable computation times and memory efficient sparse storage of these huge matrices. We have implemented FSL's White matter Hierarchical Modelling (WHIM) that aligns fiber indices across individuals and also integrated this technology into probtrackx, enabling the production of matrix4 results where fibers are directly comparable across individuals. Finally, we adapted a very fast sparse NMF algorithm to enable operation on these enormous sparse tractography matrices along with using an NMFSSO approach to cluster multiple random starts of NMF to improve NMF reproducibility. We have successfully factorized a single HCP individual at native diffusion resolution into components that match known tract bundles such as the arcuate fasciculus and future work will apply this technique on group average matrix4 data followed by non-negative dual regression into individual matrix4 connectomes. Overall, this framework brings together multiple technical advances, including in cross-individual spatial alignment, tractography methods, cross-individual fiber alignment, and non-negative matrix factorization to enable generation of a fully-data-driven precisely aligned and high resolution human structural connectome tract atlas.

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Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.03/MM4

Topic: J.07. Data Analysis and Statistics

Support: NIH R01MH60974
NIH UM1MH130981

Title: DRUMS - A Flexible New Deep Learning Tool for Precise Cortical Surface Alignment across Individuals

Authors: *Y. WANG[1], C. YANG[2], T. COALSON[2], D. C. VAN ESSEN[3], M. F. GLASSER[4]; [1]Washington Univ. in St. Louis, St. Louis, MO; [2]Washington Univ. in St. Louis, Saint Louis, MO; [3]Neurosci., Washington Univ. in St. Louis, St Louis, MO; [4]Radiology, Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Accurate inter-individual alignment of human cerebral cortex is challenging due to the high variability of human cortical folding patterns and the regionally non-uniform and inconsistent spatial relationships across individuals between cortical folds and the functional networks and cortical areas that we wish to study. To achieve precise alignment across individuals, an algorithm should use multi-modal neuroimaging features related to cortical areas and functional networks and should learn a spatially non-uniform regularization function that reflects the true gamut of human inter-individual variability in cortical organization. Ideally, it should also be capable of denoising its own input registration features to avoid overfitting to noise and should not require precise hand tuning of input regularization parameters. To address these challenges, we developed Diversely Reconstructed U-Net with Multimodal Supervision (DRUMS), a novel deep learning framework for multi-modal cortical surface registration. DRUMS implements deep-learning-based cortical surface registration on multi-resolution spheres, which is the same well-validated approach used in classical registration algorithms such as Multi-modal Surface Matching (MSM), and also includes the same physically inspired strain energy regularization that we used for MSM and the same precise barycentric interpolation on spherical surface meshes. DRUMS has a three-stage architecture: (1) multiscale feature extraction, (2) multiscale feature integration, and (3) deformation field generation. The framework's multimodal design supports flexible integration of diverse imaging modalities, enabling registration using either folding features with multi-modal supervision during training or multi-modal features as direct inputs. DRUMS outperforms Multi-modal Surface Matching (MSM), the current state-of-the-art method used in the Human Connectome Project (HCP) pipelines, over a wide range of input regularization settings in both registration accuracy and test-retest reproducibility of registration results for both supervised folding registrations and multi-modal registrations across all tested modalities, including held out modalities. DRUMS further learns a biologically plausible spatially non-uniform regularization function, with registration induced distortion correctly matched to known human inter-individual cortical variability. These results suggest that DRUMS should replace MSM in the HCP Pipelines and position DRUMS as a versatile and reliable tool for cortical surface registration in neuroimaging research.

Disclosures: Y. Wang: None. **C. Yang:** None. **T. Coalson:** None. **D.C. Van Essen:** None. **M.F. Glasser:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

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Program #/Poster #: PSTR294.04/MM5

Topic: J.07. Data Analysis and Statistics

Support: F32 Grant 1F32MH140418-01

Title: Mapping of Atypical Cortical Areal Topologies in the Human Brain

Authors: *N. DEMIRCI[1], T. COALSON[2], Y. WANG[3], D. C. VAN ESSEN[4], M. F. GLASSER[5];
[1]Washington Univ. in St. Louis Sch. of Med., St. Louis, MO; [2]Neurosci., [3]PhD in Imaging Sci., Washington Univ. in St. Louis, St. Louis, MO; [4]Neurosci., Washington Univ. Sch. Med., St Louis, MO; [5]Dept. of Anat. & Neurobio., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Previous studies using the Human Connectome Project Multimodal Parcellation version 1.0 identified atypical topologies of area 55b using MSMAll areal-feature-based registration and a multi-layer perceptron areal classifier. Area 55b was sometimes bisected by neighboring areas FEF or PEF or swapped positions with FEF. These patterns were supported across multiple underlying modalities, including myelin maps, functional connectivity, and task activation, arguing that this variability was genuine. However, the prevalence, reproducibility, and feature determinants of atypical cortical topologies across the full cortex remain largely unexplored. Here, we used an improved deep learning-based surface registration together with a refined multimodal areal classifier that maximizes reproducible individual variability to investigate atypical cortical area topologies in HCP Young Adult (HCP-YA, N=1,071, 22-35 years of age) participants. To assess reproducibility, we additionally analyzed 45 HCP test-retest individuals.Cortical areas were examined for fragmentation and alternative neighbor arrangements. For each cortical area and subject, a fragmentation index [0-1] based on mesh connectivity was computed to quantify split of an area. Zero indicated spatially contiguous areas, whereas higher values reflected multiple fragments. Areas with fragmentation indices within a predefined range [0.1-0.5] were classified as split topologies, while excluding small, isolated vertex clusters which can arise from classifier uncertainty. To evaluate whether observed splits reflect biologically meaningful topologies, the top-ranked multimodal features based on classifier feature importance and their surface gradients were analyzed. Split boundaries were aligned with strong transitions in the underlying multimodal feature maps. Preliminary results indicate robust split topology of area 55b in ~8% of participants, occurring in 41 individuals in the left hemisphere, 45 in the right hemisphere, and 4 bilaterally. Neighbor analyses showed atypical configurations also in adjacent areas such as FEF and PEF, such as 55b splitting area FEF or area PEF. Simultaneous split topologies were also observed, including cases in which both 55b and PEF or both 55b and FEF were split within the same hemisphere. Functional connectivity patterns and their gradients support these atypical configurations, indicating that these findings represent genuine biological variability. Together, these findings characterize

atypical cortical area topologies in the human brain and establish a framework for studying individual differences in cortical organization.

Disclosures: N. Demirci: None. **T. Coalson:** None. **Y. Wang:** None. **D.C. Van Essen:** None. **M.F. Glasser:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.05/MM6

Topic: J.07. Data Analysis and Statistics

Support: NIH/NIA R01 AG092088

Title: Probabilistic Functional Modes outperforms Temporal Independent Components Analysis for an fMRI atlas of weighted spatially overlapping functional networks

Authors: *K. A. YANG[1], B. Q. ROSEN[2], T. COALSON[1], H. ZHOU[3], D. C. VAN ESSEN[4], M. F. GLASSER[5];
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Abstract: Functional networks (sets of brain regions with synchronized activity fluctuations) are often mapped with fMRI using "winner-take-all" hard parcellations that assign each brain location to a single dominant network and thereby oversimplify the brain's functional organization. Weighted, spatially overlapping decompositions capture this organization more faithfully, but the most widely used approach, spatial independent component analysis (sICA) constrains components to be spatially uncorrelated, which is neurobiologically implausible. Temporal ICA (tICA) and probabilistic functional modes (PFM, or PROFUMO) both relax this constraint (though tICA enforces temporal orthogonality), yet it remains unclear which better supports a reproducible and neurobiologically interpretable atlas. Using high-quality fMRI from the Human Connectome Project Young Adult dataset (3 Tesla, n=1071; 7 Tesla, n=175) across resting, traditional repetitive tasks, movie, and retinotopy states, we compared tICA and PFM to determine which yields a more suitable atlas. We evaluated three dimensions: (1) reproducibility across two independent groups (n=475 each), within test-retest individuals (n=45), and across imaging states, using hierarchical clustering to group corresponding components into cross-state "families"; (2) neurobiological interpretability, by spatially correlating component maps to group-level task general linear model (GLM) activations; and (3) individualization, by the same GLM comparison at the single-subject level. At the group and individual levels, tICA and PFM showed comparable reproducibility, interpretability, and individualization, with tICA holding a slight advantage in some task comparisons. However, tICA tended to split single networks into

multiple subcomponents to enforce temporal independence, producing more fragmented correlation structure, whereas PFM yielded cleaner, more coherent component correspondence. PFM also showed stronger cross-state reproducibility, identifying more multi-state component families, and a more stable network structure. Although both methods perform similarly overall, PFM's greater cross-state consistency and more coherent structure make it more suitable for constructing a reproducible and neurobiologically interpretable atlas of weighted, spatially overlapping functional networks

Disclosures: K.A. Yang: None. **B.Q. Rosen:** None. **T. Coalson:** None. **H. Zhou:** None. **D.C. Van Essen:** None. **M.F. Glasser:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.06/MM7

Topic: J.07. Data Analysis and Statistics

Support: Neurtex Brain Research Institute

Title: Changes in random background activity can produce apparent single-neuron responses after spike sorting

Authors: *P. N. STEINMETZ[1], J. T. WIXTED[2];
[1]NeurTex Brain Res. Inst., Dallas, TX; [2]Psychology, UC San Diego, La Jolla, CA

Abstract: The detection and clustering of large voltage excursions in extracellular recordings is a pivotal neurophysiological technique for identifying the activity of putative single neurons, which are then examined for responses to experimental manipulations. However, such voltage excursions can also arise from random background activity generated by large numbers of neurons or other noise sources, potentially producing false-positive responses (FPRs).
To estimate FPR rates, we simulated a typical human intracranial microwire recording experiment in which a general change in background activity occurred on 192 of 792 one-second trials, corresponding to responses to one or more of 33 simulated presented objects. We then applied commonly used spike-sorting techniques to isolate putative single-unit activity and tested whether firing rates depended on simulated object identity.
Across representative simulations, changes in background activity produced spurious object effects after spike sorting. With BML spike sorting, a 4% increase in background activity produced a median object effect size of $\eta^2 = 0.053$, with 37% of sorted units showing a significant object effect on firing rate (one-way ANOVA, $p < 0.05$). With WaveClus, a larger 33% increase produced a median effect size of $\eta^2 = 0.25$, with 100% of sorted units showing a significant object effect.
We also tested for changes in background activity independent of apparent single-unit activity by measuring the standard deviation (STD) of voltage samples after excluding times around

detected spikes. This test was highly sensitive to background changes, yielding $\eta^2 = 0.36$ for a 4% STD increase. Reanalysis of prior human intracranial microwire recordings showed that comparable background changes are also present in real recordings.
Thus, modern spike-sorting methods are sensitive to changes in background activity even when no explicit single-neuron activity is present. Such background changes can be detected independently and used to evaluate the quality of putative single-neuron responses. These results are consistent with other work showing that general activity changes can be predicted from local field potentials and used to control neuroprosthetic devices.

Disclosures: P.N. Steinmetz: None. **J.T. Wixted:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

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Program #/Poster #: PSTR294.07/MM8

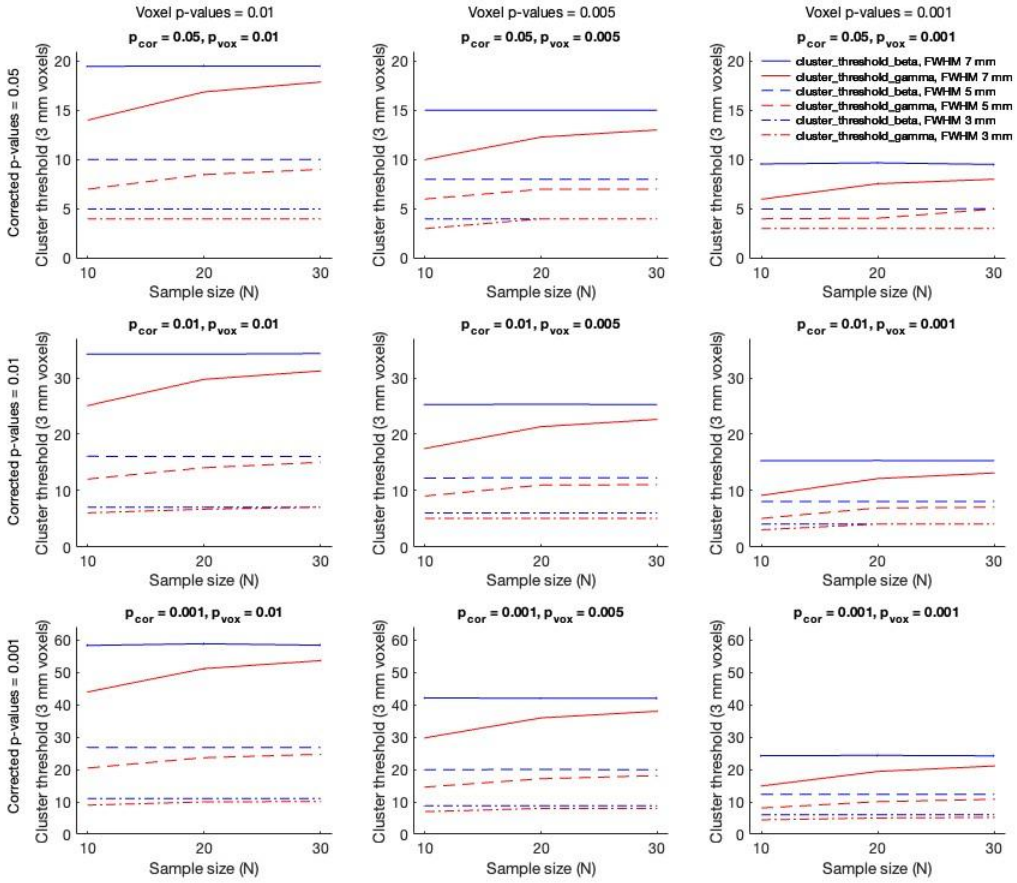
Topic: J.07. Data Analysis and Statistics

Title: Reducing type II error in fMRI analysis: Cluster-extent threshold simulation results and an evaluation of current methods to correct for multiple comparisons

Authors: *S. D. SLOTNICK;
Boston Col., Chestnut Hill, MA

Abstract: Many procedures to correct for multiple comparisons in fMRI analysis require a minimum cluster-extent threshold; however, sample size (N) is often not modeled. For example, in the MATLAB script cluster_threshold_beta, Monte Carlo simulations are conducted with brain activity modeled by random values with Gaussian spatial autocorrelation, and the minimum spatial extent of contiguous activity across simulations is computed to correct for multiple comparisons. In this study, a series of simulations was conducted using a new MATLAB script cluster_threshold_gamma, where N was varied to determine whether this parameter affected cluster threshold. The primary hypothesis was that modeling N in the simulations would reduce cluster thresholds. Another hypothesis was that this cluster size reduction was due to between-subject variability, which was tested by eliminating the corresponding standard error term. Acquisition volume parameters were fixed, while the following key parameters were varied: N (10, 20, or 30), corrected p-value (.05, .01, or .001), individual-voxel p-value (.01, .005, or .001), FWHM (3, 5, or 7 mm), and voxel resolution (2 or 3 mm). Each simulation consisted of 100 iterations repeated 100 times, with a total of 4,860,000 iterations and 66,420,000 simulated subjects. There was a significant effect of condition with clusters approximately 18% smaller with versus without N modeled and a significant increase in cluster thresholds for larger sample sizes, as shown in Figure 1 (cluster-extent thresholds produced by cluster_threshold_beta, in blue, and cluster_threshold_gamma, in red; key at the top right). Bayesian analysis provided very strong support for the secondary hypothesis. These simulation results were replicated in a real fMRI data set. The present findings indicate that

sample size should be incorporated into all methods to provide the most accurate thresholds possible and reduce type II error. A broader range of topics is discussed including balancing type I and type II error, and the assumption that non-task fMRI activity reflects null data is questioned.



Disclosures: S.D. Slotnick: None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.08/MM9

Topic: J.07. Data Analysis and Statistics

Support: Brain Aneurysm Foundation Award

Title: Multimodal Discrete-Time Hazard Modeling Using Within-Patient Normalized EEG for Predicting Delayed Cerebral Ischemia After Aneurysmal Subarachnoid Hemorrhage

Authors: *Z. JIN[1], K. LYMAN[2], E. GILMORE[3], B. WESTOVER[4], J. KIM[5];
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Abstract: Background: Delayed cerebral ischemia (DCI) is a major cause of morbidity following aneurysmal subarachnoid hemorrhage (aSAH). Continuous EEG may provide early evidence of evolving cerebral dysfunction, but optimal longitudinal EEG representations and the value of multimodal integration remain unclear. We evaluated discrete-time hazard models for imminent DCI using patient-specific EEG normalization alone and combined with clinical and imaging features.
Methods: Risk-set samples were constructed from 48-240 hours after hemorrhage. Labels indicated DCI onset within future hazard windows of 6-24 hours. EEG predictors included global, vascular-territory, and hemispheric-asymmetry quantitative EEG features. We compared absolute EEG values, rolling baseline ratios, and fixed-baseline ratios. Multimodal models incorporated Hunt-Hess grade, modified Fisher score, EHR-derived clinical features, and imaging volume features. Balanced bagged random forests were evaluated using repeated patient-level cross-validation.
Results: Fixed-baseline normalization consistently outperformed absolute EEG values and rolling baseline approaches, suggesting that patient-specific reference states better capture evolving pathophysiological changes preceding DCI. This finding highlights the importance of within-patient normalization for longitudinal EEG biomarker development. Among 117-137 Yale New Haven Hospital aSAH patients, the 60-66 hour fixed-baseline representation yielded the strongest overall performance for 9-hour hazard prediction, achieving a mean AUROC of 0.57 across all evaluated time points and a peak AUROC of 0.78 at 156 hours after hemorrhage. In multimodal analyses (54-66 patients), the best-performing model combined EEG, clinical, and imaging features using the 66-72 hour baseline window for 9-hour hazard prediction, achieving a mean AUROC of 0.62 across all evaluated time points and a peak AUROC of 0.86 at 162 hours after hemorrhage. These findings suggest that integrating longitudinal neural recordings with complementary clinical and imaging data may improve prediction of impending neurological deterioration.
Conclusions: Discrete-time hazard modeling enables temporally resolved prediction of imminent DCI after aSAH. Patient-specific EEG normalization improves predictive performance, and multimodal integration further enhances discrimination. These findings support development of individualized, time-resolved DCI risk monitoring tools for neurocritical care and future prospective clinical evaluation.

Disclosures: Z. Jin: None. **K. Lyman:** None. **E. gilmore:** None. **B. Westover:** None. **J. Kim:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.09/MM10

Topic: J.07. Data Analysis and Statistics

Title: Introducing the DDG ('Dodeconogram') - A next-generation EEG platform that acquires 12 parallel scalp frequency bands from 1 hertz to 5 gigahertz.

Authors: *S. R. HAMEROFF[1], A. BANDYOPADHYAY[2], P. SINGH[3];
[1]Quantum Life Technologies, San Francisco, CA; [2]NIMS, Tsukuba, Japan; [3]IIT Mandi, Himachal Pradesh, India

Abstract: Deeper, faster coherent electrodynamic signals ‘buried’ in EEG have been discovered in the brain. The Dodecanogram (DDG) is a noninvasive, next-generation EEG platform that acquires 12 parallel scalp frequency bands from 1 Hz to 5.31 GHz while preserving cross-band timing and phase from the front end onward. Each probe combines a miniaturized Yagi antenna array, a saline sponge interface, and a silver-nanoparticle-functionalized silicon substrate that acts as a passive plasmonic near-field concentrator before band-selective analog conditioning and synchronized comparator-based digitization. In proof-of-concept human recordings obtained during baseline, meditation, chanting, talking, sadness, and anger, DDG produced reproducible task-linked multiband burst, phase-locking, and connectivity patterns. Low-arousal states showed reduced broadband recruitment and more stable phase organization, whereas high-arousal states showed stronger multiband activity, shorter-lived phase groupings, and more frequent phase slips.These results support DDG as an experimental platform for testing cross-scale phase organization and candidate electrophysiological biomarkers that complement amplitude-focused EEG analyses, while motivating larger studies with shielding, phantom controls, and expanded subject cohorts to distinguish neural signals from environmental and interface artifacts.

Disclosures: S.R. Hameroff: None. **A. Bandyopadhyay:** None. **P. Singh:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.10/MM11

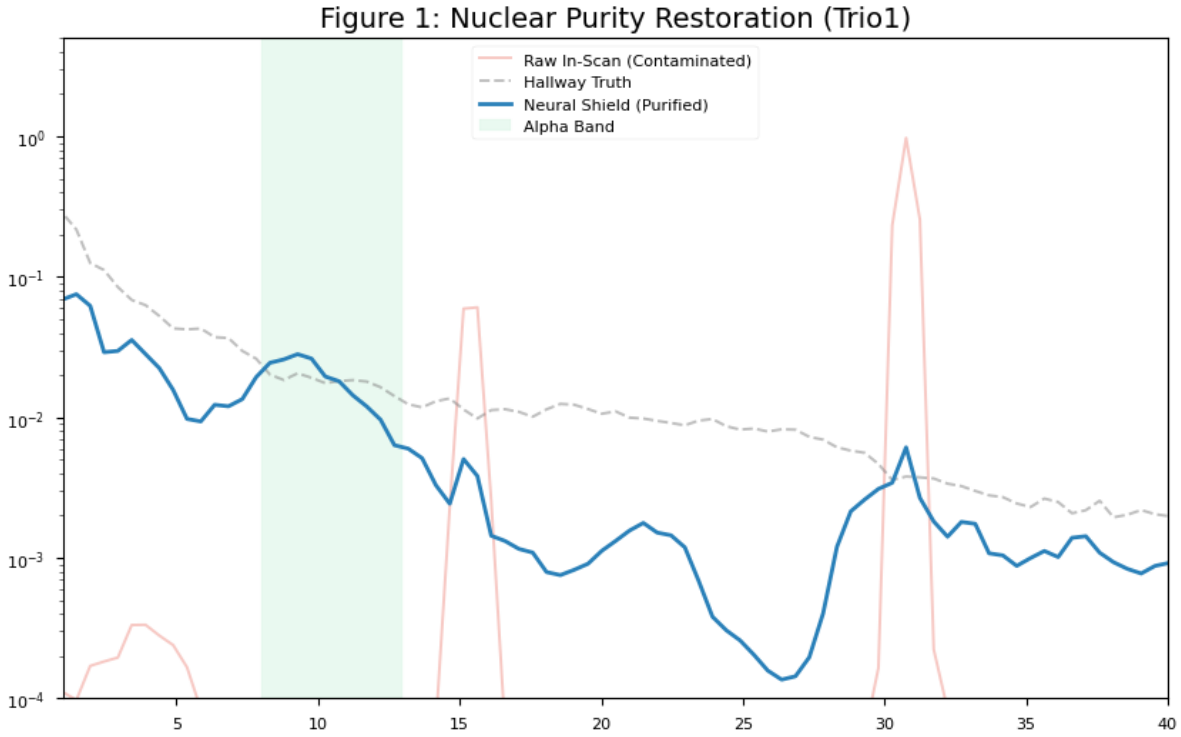
Topic: J.07. Data Analysis and Statistics

Title: CWL-free BCG suppression for clinical EEG-fMRI using ECG-driven deep learning

Authors: *A. TEHRANI;
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Abstract: Simultaneous EEG-fMRI recording is affected by ballistocardiogram (BCG) artifacts and reference carbon wire loops (CWLs). BCG corrupts brainwaves while CWL injects environmental noise, limiting 0.55T EEG-fMRI applicability in clinical practice. Conventional

ICA displays component bleeding in the alpha band (8-13 Hz), where components marked for rejection as "artifacts" like BCG may carry relevant neurophysiological info. In this study, we aim to remove unwanted BCG artifacts while retaining desired neurophysiological information using a 1D NN (NeuralShield). NeuralShield was designed to use standard ECG leadset at inference for enhanced generalizability. The network was trained on 3T recordings (NITRC dataset) using CWL reference signals as target maps for nonlinear ECG to artifact mapping. Latent representation was constrained to 16 units and a PCA interaction tensor was used to model structures associated with ECG-induced artifact. The 8-13 Hz frequency range was excluded from Ridge regression loss function to avoid fitting biological alpha rhythms. Additionally, we used a 15 Hz cutoff to model suppressed non-physiological high frequency noise learned during training on hardware, such as 30 Hz vibrations of a helium pump. Using a 3T dataset of 8 subjects and 14 eyes open/closed sessions, we obtained alpha-band SNR improvement of +14.85 dB (paired t-test, $p<0.05$), comparable to the supervised baseline that provided +14.63dB. Correction using physical CWL or ICA achieved inferior +1.56 dB and +0.42 dB, respectively. Such studies provide a picture of how ECG-only inference eliminates physical sensor dependencies and removes hardware barriers to clinical EEG-fMRI.



Disclosures: A. Tehrani: None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.11/MM12

Topic: J.07. Data Analysis and Statistics

Support: NSF 2340997
NSF 2349771

Title: EEG-Based Neural Signatures of Active Deception: Evaluating Time-Frequency vs. Deep Latent Representations in Visual-Spatial Authentication

Authors: *S. SUNDAR[1], P. GYREYIRI[2], D. SHUKLA[3];
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Abstract: Reliable user authentication remains a critical challenge in digital security. Although traditional biometric models are designed to reject generic irregularities, secure systems must also withstand active and targeted deception. This study introduces an EEG-based approach that investigates the specific neural dynamics differentiating authentic visual-spatial memory retrieval from the cognitive burden of targeted mimicry. In this study, twenty-eight (28) volunteer participants each created a personalized visual stimulus by selecting a familiar face and placing it within a symmetrical n×n two-dimensional grid. Each participant completed two EEG recording sessions, with 30 trials each, spaced 5-7 days apart. During the second session, participants underwent a targeted "impostor" paradigm: they were assigned two "victims," instructed to explicitly memorize their specific visual cue, and subjected to authentication trials designed to mimic those targeted victims. EEG data were recorded using the 18-channel DSI-24 headset. The recorded data were segmented into 0.9-second stimulus-locked epochs and evaluated using two distinct analytical pipelines: a traditional global spatial-spectral feature extraction and a deep learning approach utilizing 2-channel Spectrogram and Continuous Wavelet Transform (CWT) time-frequency maps. Differentiating authentic recall from targeted mimicry proved highly dependent on observing broadly distributed network topology rather than localized frequency bursts. A baseline classification utilizing traditional engineered global features was successfully able to discriminate against genuine responses from impostor attacks with a mean Equal Error Rate (EER) of 0.386. Emerging techniques such as deep neural networks can be utilized to extract nuanced discriminating features, potentially improving performance further. These findings demonstrate that the cognitive load of targeted mimicry (actively holding a counterfeit sequence in working memory while suppressing authentic recall) relies on complex, brain-wide neurophysiological states instead of easily isolated spectral-temporal artifacts. Funding: This work was supported in part by the National Science Foundation (NSF) under Grants 2340997 and 2349771.

Disclosures: S. Sundar: None. **P. Gyreyiri:** None. **D. Shukla:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.12/MM13

Topic: J.07. Data Analysis and Statistics

Title: Effects of Echo Time and Multi-Echo Processing on Resting-State Network Decoding: Implications for Negative BOLD Activity

Authors: *A. C. FELDBUSH[1], J. SOLDATE[2], S. M. LACONTE[3];
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Abstract: The Default Mode Network (DMN) is one of the most widely studied resting-state networks, yet the physiological basis of its characteristic negative blood-oxygen-level-dependent (BOLD) response remains unclear. Unlike positive BOLD, which is associated with increased neural activity and signal increases during task performance, the DMN is frequently suppressed during externally directed tasks. Here, we use multi-echo fMRI in combination with multivariate supervised learning to decode negative BOLD DMN signals. Because the BOLD contrast is TE-dependent, multi-echo fMRI provides a unique opportunity to compare the physiological properties of networks associated with positive and negative BOLD responses. In particular, the TE dependence of DMN decoding may offer insight into the mechanisms underlying negative BOLD activity.Using the Non-parametric Predictive Accuracy and Reproducibility (NPAIRS) framework and an open-access resting-state fMRI dataset (n=301), we quantified how echo time and multi-echo analysis approaches affect our ability to decode the DMN and other networks.Compared to other resting state networks, echo time had a significant effect on DMN decoding. Somatosensory and DMN showed particularly strong echo-time sensitivity, with longer TEs generally improving performance. In contrast, limbic and cerebellar networks favored shorter echo-times. Combining echoes reduced this variability, but not equally across strategies. TEDANA's T2*-weighted "optimal" combination showed significantly lower prediction accuracy than individual echoes at TE»30ms and 47ms ($p = 5.28\times10^{-10}$ and $p = 2.13\times10^{-11}$, respectively), despite its producing higher temporal signal-to-noise ratio (tSNR). Simpler approaches (i.e., echo summation and tSNR-weighted combination) substantially outperformed TEDANA ($p = 9.80\times10^{-27}$ and $p = 3.71\times10^{-21}$, respectively).The pronounced TE dependence observed in the DMN, which was among the most TE-sensitive networks, suggests that negative BOLD signals may be more strongly influenced by TE-dependent contrast mechanisms than many networks characterized predominantly by positive BOLD responses. These findings highlight the potential of multi-echo fMRI to disentangle physiological differences between negative and positive BOLD while also revealing a critical dissociation between tSNR and machine learning performance. Specifically, preprocessing strategies that maximize signal quality do not reliably improve, and may actively impair, network-level decoding. Thus, “optimal” multi-echo preprocessing may not be universal and should be selected according to the scientific question being addressed.

Disclosures: A.C. Feldbush: None. **J. Soldate:** None. **S.M. LaConte:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.13/MM14

Topic: J.07. Data Analysis and Statistics

Support: President's Excellence in Research Scholars (PERS), Tarleton State University

Title: Generalizable Individual Phoneme Classification with EEG

Authors: *N. SOLAGRATIA, D. W. GATLIN, G. OSEI, L. N. REBOLLAR-HERNANDEZ, A. DAVILA, D. DASH;
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Abstract: Speech-brain computer interfaces (speech-BCIs) translate brain activity to speech, assisting in communication for individuals with neurologic disorders (e.g. ALS). Non-invasive methods, such as electroencephalography (EEG), have been demonstrated to decode imagined or overt speech (e.g. phonemes). However, most non-invasive studies are limited to small phoneme sets (mostly pair-wise classifications) and small participant sizes (mostly subject-dependent). Expanding the phonetic vocabulary in EEG systems degrades the signal-to-noise ratio, resulting in poor decoding performance. This study investigates the reliability of decoding 9 English phonemes from EEG signals using both subject-dependent and subject-independent evaluation. Using a 64-channel EEG dataset collected from 24 participants, we developed a phoneme decoding pipeline consisting of spatial, spectral, and temporal feature extraction and evaluation across 26 classical machine learning algorithms and 8 deep learning architectures. We achieved a 9-class subject-dependent classification accuracy of 34.34% ± 1.69% using log-eigen values of the broadband EEG spatial covariance matrix feature (log_eigen_covar), which significantly outperformed all evaluated time-domain features (mean, variance, covariance, kurtosis, and root mean square) (1-way ANOVA, $F = 218.62$, $p < 0.001$, post-hoc Tukey test $p < 0.001$). Spectral analysis revealed a significant effect of neural oscillations on classification performance with broadband EEG (0.1 - 100 Hz) yielding the highest overall accuracy (1-way ANOVA, $F = 16.31$, $p < 0.001$), outperforming high-gamma (62.5 - 100 Hz; $p < 0.01$), delta (0.0 - 3.9 Hz), theta (3.9 - 7.8 Hz), and alpha (7.8 - 15.6 Hz) bands (post-hoc Tukey tests, $p < 0.001$). No statistically significant differences were observed between broadband and beta (15.6 - 31.25 Hz) or gamma (31.25 - 62.5 Hz) bands, which achieved accuracies of 32.86% ± 1.74% and 32.63% ± 1.59%, respectively. Subject-independent evaluation achieved 39.39% ± 4.48% accuracy with leave-one-subject-out cross-validation across 24 subjects when broadband spectrum was trained with a 2D-CNN-LSTM model. Overall, these results demonstrate that EEG signals contain decodable multi-class phonetic information and provide a foundation for future generalizable non-invasive speech-BCI development.

Disclosures: N. Solagratia: None. **D.W. Gatlin:** None. **G. Osei:** None. **L.N. Rebollar-Hernandez:** None. **A. Davila:** None. **D. Dash:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

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Program #/Poster #: PSTR294.14/MM15

Topic: J.07. Data Analysis and Statistics

Support: R01HD114489

Title: Dense longitudinal neuroimaging: test-retest reliability of monthly diffusion MRI in young children

Authors: *S. BUETTNER[1], X. REN[2], G. AMOROSINO[3], F. PESTILLI[4], K. SCHILLING[5], S. VINCI-BOOHER[2];
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Abstract: Characterising individual trajectories of rapid white matter changes requires dense longitudinal neuroimaging (DLN) - repeated sampling of the same individual across what are often short windows of rapid brain change. Because DLN must often detect small between-session changes, a critical challenge is establishing the noise floor: how much between session variation in diffusion metrics can be attributable to measurement error alone, below which biological change cannot be reliably detected? Here, we quantified the noise floor for fractional anisotropy (FA) in a monthly DLN study of first-grade children using multi-shell diffusion MRI (b = 1000, 2000 s/mm2, 2.5 mm isotropic). At the 12th and final session, children completed an additional diffusion run (retest) that was separated from the session run (test) by out-of-scanner repositioning. Diffusion data were preprocessed using an MRtrix3-based pipeline. Participant-specific tractograms were generated for the test run and applied to tensor-based FA maps for all sessions and the retest run at the final session using a tract profiles approach. Tract-level FA was computed by averaging across individual tracts after excluding tract endpoints to account for partial voluming. First, voxel-wise FA was highly reliable between test-retest runs (r = .85 and .90, both $p < .001$). Second, test-retest FA differences at the tract-level were approximately 1-2% compared to approximately 3-4% for monthly between-session differences. Critically, DLN changes exceeded the noise floor, supporting their interpretation as true biological change. Together, these results address a critical challenge for DLN designs by providing an empirical demonstration that monthly DLN diffusion measurements in young children exceed the noise floor and, more broadly, provide a benchmark for detecting meaningful white matter changes using diffusion imaging in young children.

Disclosures: S. Buettner: None. **X. Ren:** None. **G. Amorosino:** None. **F. Pestilli:** None. **K. Schilling:** None. **S. Vinci-Booher:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.15/MM16

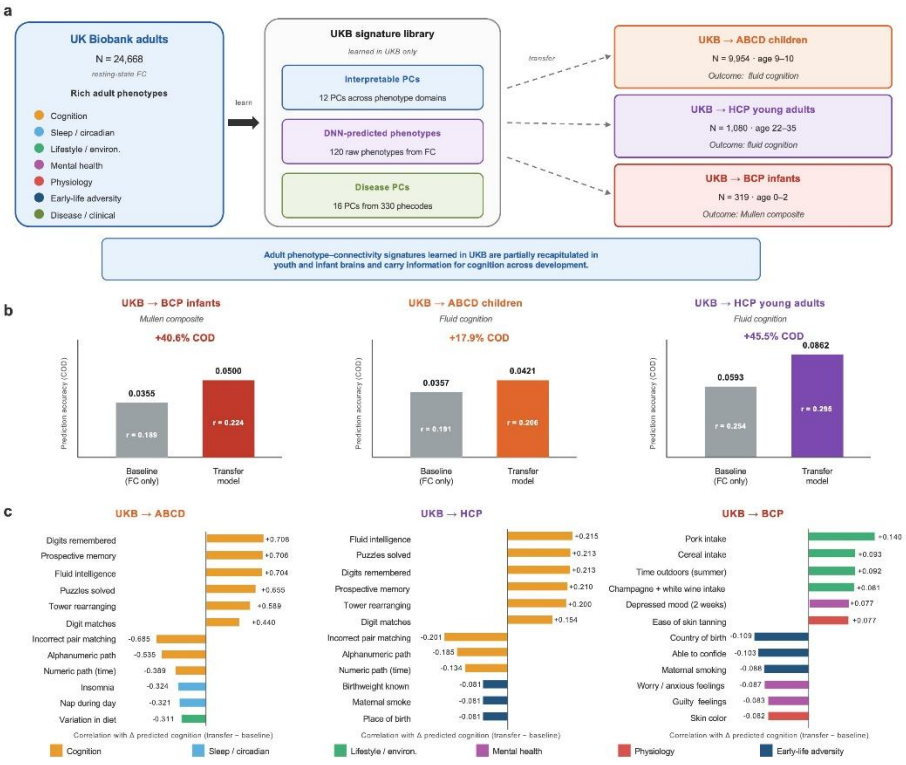
Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R21HD120911
NIH Grant K01AG095286
NIH Grant R01MH136055

Title: Adult Brain Connectivity Signatures Trace Back Across the Lifespan to Infancy

Authors: *S. WANG, W. YIN, Z. WU, G. LI, W. LIN, T. LI;
Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: A central question in developmental neuroscience is whether brain signatures linked to adult cognition, behavior and risk are already present early in life. We tested whether resting-state functional-connectivity (FC) patterns learned from adult phenotypes are recapitulated in younger brains and carry information about cognition. We developed a cross-age, cross-cohort meta-matching framework in a shared FC space. All cohorts were harmonized with the UK Biobank pipeline and ICA-100 atlas, retaining 55 quality-controlled components and 1,485 FC edges. Baby Connectome Project (BCP) infant scans were preprocessed with iBEAT V2.0 and registered to the MNI152 space. In 24,668 UKB adults, we learned phenotype-connectivity signatures spanning cognition, lifestyle, mental health, physiology, early-life factors and clinical phenotypes such as disease status from 330 ICD10 phecodes. These adult-derived signatures were transferred to three younger cohorts: 9,954 ABCD children aged 9-10 years, 1,080 HCP-Young participants aged 22-35 years and 319 BCP infants aged 0-2 years. Cognition targets were fluid cognition in ABCD and HCP-Young and Mullen composite in BCP, predicted using an ensemble of kernel ridge regression and deep neural network models. Adult signatures improved prediction over an FC-only baseline in every cohort. Coefficient of determination increased from 0.0357 to 0.0421 in ABCD (+17.9%), from 0.0593 to 0.0862 in HCP-Young (+45.5%) and from 0.0355 to 0.0500 in BCP infants (+40.6%; r = 0.189 to 0.224). In children and young adults, gains were driven mainly by cognition-related signatures. In infants, contributing signatures were weaker and distributed across lifestyle, early-life, mental-health and physiological domains. These findings suggest that adult phenotype-related FC signatures are partly recapitulated in infancy and already contain information about early cognition. Cross-age meta-matching provides a way to trace developmental origins of brain phenotypes that cannot be measured directly in early life.



Disclosures: S. Wang: None. **W. Yin:** None. **Z. Wu:** None. **G. Li:** None. **W. Lin:** None. **T. Li:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.16/MM17

Topic: J.07. Data Analysis and Statistics

Title: A cross-attention model for discovering dynamic interaction patterns in multimodal EEG-fMRI fusion

Authors: *M. HOSSEINI, C.-H. MIN;
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Abstract: Multimodal neuroimaging approaches capture different perspectives on brain function through modalities such as electroencephalography (EEG) and functional magnetic resonance

imaging (fMRI). Each modality has its different characteristics across temporal, spectral, and spatial resolutions. Numerous studies have shown that machine learning models can effectively capture multimodal brain patterns. However, their interpretability remains a key challenge, particularly in understanding how they learn interactions across complementary modalities. These interactions are often not directly interpretable, limiting insight into information flow within and across modalities. This highlights the importance of developing interpretable multimodal machine learning methods as a promising approach for uncovering clearer insights into brain function. In this study, we extend our previous work by developing a cross-attention classifier that processes neuroimaging data to learn task-specific representations. The model assigns adaptive weights to different modalities to optimize classification performance. Importantly, the learned cross-attention weights reveal cross-modal interactions, providing deeper insights into brain state signatures. We evaluate our model on a freely available joint EEG-fMRI sleep stage dataset recorded from 33 participants. We extract functional connectivity features from 32-channel EEG and averaged covariance matrices from fMRI BOLD data based on 132 brain regions defined by the Harvard atlas. Results from 10 independent runs demonstrate that the proposed model detects stable activation patterns across repeated stochastic training, where stability is quantified as the ratio of the mean cross-attention weight to its standard deviation across runs, reflecting the consistency of learned EEG-fMRI relationships. This analysis revealed reproducible coupling patterns in the cerebellar vermis (Ver10; stability = 1.13) within fMRI data and in CP2-centered centroparietal EEG regions (CP2; stability = 1.36) during transitions between REM2 and awake states. These findings suggest that the proposed approach can effectively uncover complex brain state patterns in an interpretable manner, with minimal reliance on extensive manual analysis in multimodal neuroimaging research.

Disclosures: M. Hosseini: None. **C. Min:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

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Program #/Poster #: PSTR294.17/MM18

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R00HD103873

Title: Small Heads, Big Challenges: Data-Driven MRI Quality Control and Demographic Predictors of Scan Quality in Preschoolers

Authors: *A. BHUVANAPALLI[1], G. ABDUROKHMONOVA[1], A. MORTIMER[1], R. ROMEO[2];
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Abstract: Quality control (QC) of magnetic resonance imaging (MRI) data is essential for reliable, reproducible neuroimaging. MRIQC is a standardized, data-driven QC pipeline that provides Image Quality Metrics (IQMs) for structural and functional MRI. However, existing MRIQC classifiers are largely trained on adult datasets, raising concerns about their applicability to preschool populations.We examined how developmental and behavioral factors influence MRIQC-derived IQMs in preschool-aged children. We analyzed T1 data from N=60 participants (ages 3-5) in an ongoing longitudinal study. Motion-sensitive IQMs — including the coefficient of joint variation (CJV), contrast-to-noise ratio (CNR), entropy focus criterion (EFC), and full-width at half maximum (FWHM) — were analyzed in relation to age, sex, socioeconomic status, and race. QC outcomes were compared across three data-driven approaches: cohort-specific thresholding, MRIQC API-informed thresholding, and the MRIQC Random Forest Classifier (RFC).Age and race were significant predictors of scan quality. Younger age predicted higher CJV ($\beta = -1.244$, $p = 0.036$), and Black, Hispanic/Latino, and multiracial participants exhibited disproportionately lower image quality, characterized by higher CJV and EFC and lower CNR.QC methods differed substantially in participant inclusion. The RFC showed poor generalizability to preschool data, assigning a 100% pass rate. Thresholding methods identified the same excluded participants, though MRIQC API-informed thresholds were more conservative (60.0% pass rate) than cohort-specific thresholds (83.3%). Manual QC was the most exclusionary (38.3% pass rate) and differed from all data-driven methods in those excluded.Manual QC decisions were most associated with CJV ($r = -0.72$) and CNR ($r = 0.72$), metrics that also showed the greatest demographic variation. In contrast, threshold-based approaches relied more on SNR and FWHM, which were less demographically sensitive.These findings suggest that IQM and QC outcomes in preschool MRI are shaped by both developmental and demographic factors, highlighting the need for pediatric-specific, bias-conscious QC frameworks. Age-appropriate QC standards may reduce sampling bias and improve the generalizability of developmental neuroimaging research.

Disclosures: A. Bhuvanapalli: None. **G. Abdurokhmonova:** A. Employment/Salary (full or part-time):; University of Maryland. **A. Mortimer:** A. Employment/Salary (full or part-time):; University of Maryland. **R. Romeo:** A. Employment/Salary (full or part-time):; University of Maryland.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

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Program #/Poster #: PSTR294.18/MM19

Topic: J.07. Data Analysis and Statistics

Support: Secretaría de Ciencia, Humanidades, Tecnología e Innovación, México. CVU:1321191

Title: Analysis of White Matter Changes in Individuals with Obsessive-Compulsive Disorder Using Two MRI Analysis Techniques

Authors: *B. CORONA MÁRQUEZ[1], R. MERCADILLO[2], L. CONCHA[3], S. ALCAUTER[4], C. ROSALES MONDRAGÓN[5], E. PASAYE[6];
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Abstract: Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric disorder that significantly affects the quality of life of those who suffer from it. It is characterized by the presence of intrusive, unwanted, and distressing thoughts or images (obsessions), which may be accompanied by repetitive behaviors performed according to specific rules (compulsions). Symptoms affect important areas of functioning such as work and interpersonal relationships and approximately half of those who suffer from it do not respond to existing treatments, so understanding its pathophysiology is essential to improving current interventions. The use of techniques such as Magnetic Resonance Imaging (MRI) in the study of individuals with OCD has revealed differences in both gray and white matter compared with control subjects. However, white matter tract analysis has received less attention, and most studies have employed diffusion tensor model-based techniques, such as Tract-Based Spatial Statistics (TBSS), which have limitations in resolving crossing fibers within the same voxel. Furthermore, previous findings have been inconsistent. To address these limitations, alternative approaches based on spherical deconvolution have been developed, like Fixel-Based Analysis (FBA), although it has been little used in the analysis of individuals with OCD.
Therefore, the aim of this research was to analyze white matter differences between individuals with OCD and control subjects using both TBSS and FBA techniques. For this purpose, diffusion-weighted MRI scans of 33 Mexican participants with OCD and 28 age- and sex-matched controls were analyzed. Images were acquired using a 3T General Electric scanner. TBSS and FBA techniques were used for analysis.
The TBSS analysis results showed widespread changes in the white matter of individuals with OCD. Overall, the findings were mostly contradictory to those reported in other studies, which may be due to the effects of therapeutic interventions or the age of symptom onset in the participants. The FBA study showed a greater density of fibers and diameters in fiber bundles in participants with OCD, concentrated in certain regions. The combined use of these analysis techniques points to an increase in white matter in participants with OCD, which could represent the effect of increased neuronal connectivity and activity, processing speed, or compensatory mechanisms. The study's conclusions should be interpreted with caution, as diffusion tensor metrics are not associated with any specific physiological or pathological process. Furthermore, adjustments to the MRI acquisition protocol are required for reliable FBA analysis.

Disclosures: B. Corona Márquez: None. **R. Mercadillo:** None. **L. Concha:** None. **S. Alcauter:** None. **C. Rosales Mondragón:** None. **E. Pasaye:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.20/MM21

Topic: J.07. Data Analysis and Statistics

Support: 1 UH3 NS119844-01A1/NH/NIH HHS

Title: Within-Subject Hemispheric Differences in Cardiac Artifact Contamination from Bilateral Dual-Target Deep Brain Stimulation

Authors: *J. GOMEZ[1], G. LOWOR[2], M. OKUN[1], A. GUNDUZ[3], K. FOOTE[1];
[1]Univ. of Florida, Gainesville, FL; [2]Univ. of Florida, GAINESVILLE, FL; [3]Biomed. Engin., Univ. of Florida, Gainesville, FL

Abstract: Cardiac (ECG) artifacts are a known source of signal contamination in deep brain stimulation (DBS) local field potential (LFP) recordings, particularly in low-frequency bands implicated in tic generation in Tourette syndrome (TS). While artifact prevalence has been described in chronic DBS recordings, whether ECG contamination differs systematically across hemispheres or targets within the same patient remains poorly characterized. We characterized within-subject hemispheric differences in cardiac artifact contamination in eight participants with TS implanted bilaterally with Medtronic Percept™ PC neurostimulators and SenSight™ leads targeting both the centromedian (CM) thalamic nucleus and the anterior globus pallidus interna (aGPi). Resting-state BrainSense Survey LFPs were acquired with stimulation OFF (~20 seconds per contact pair). Cardiac artifacts were quantified using an artifact signal-to-noise ratio metric derived from time-domain template subtraction and evaluated across all available bipolar contact pairs. Analyses were repeated using stimulation-compatible sensing configurations to assess contact pairs relevant to adaptive DBS. A total of 499 CM and 475 aGPi bipolar recordings with quality-checked cardiac artifacts were analyzed. CM recordings showed significant hemispheric asymmetry, with left-sided leads exhibiting greater cardiac contamination than right-sided leads (Wilcoxon test, FDR-corrected $p = 0.002$). This effect persisted when analyses were restricted to stimulation-compatible pairs (t-test, FDR-corrected $p = 0.001$). In contrast, aGPi recordings showed no significant hemispheric differences across all contact pairs (FDR-corrected $p = 0.309$) or stimulation-compatible configurations (FDR-corrected $p = 0.855$). Subject-level analyses revealed inter-individual variability in overall artifact burden; however, the left-sided predominance in CM recordings remained evident at the group level. These findings reveal a reproducible, target-specific hemispheric asymmetry in cardiac artifact contamination, with left CM recordings demonstrating greater susceptibility than right CM recordings, whereas aGPi recordings remained comparatively symmetric. Although right subclavicular neurostimulator placement is often selected to reduce susceptibility to cardiac artifacts, our results suggest that the impact of the neurostimulator implantation site should not be assumed uniform across different nuclei. This target-dependent vulnerability has important implications for biomarker reliability, contact selection for sensing, and the design of future adaptive DBS systems.

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Poster

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Program #/Poster #: PSTR294.21/MM22

Topic: J.07. Data Analysis and Statistics

Support: NIH ZIAMH002783
NIH ZICMH002968

Title: Optimizing data decomposition methods for multi-echo fMRI denoising

Authors: *M. M. SMITH[1], D. A. HANDWERKER[2], K. LAM[2], J. GONZALEZ-CASTILLO[2], F. PEREIRA[2], C. WALSH[2], T. MORGAN[2], P. BANDETTINI[2];
[1]NIMH, Washington, DC; [2]NIMH, Bethesda, MD

Abstract: ICA is used to denoise fMRI data by separating it into statistically independent spatial components and removing non-neural signal. Selecting the number of components to divide data into is critical, as over-separation can lead to overfitting and under-separation can harm artifact removal. Theoretically, the optimal number of components should match the underlying dimension of the data. Established dimensionality estimation methods use different criteria to determine dimension and sometimes fail. To address this challenge, we compared the reliability and plausibility of a range of methods and then tested a range of component numbers against a practical definition of optimal: improved CNR with minimal statistical cost. We selected a subset of dimensionality estimation methods from GIFT, MELODIC, and a modified version of a bootstrapping method. We tested various cost functions on a dataset of multi-echo fMRI data from 25 subjects during two tasks. Subjects completed a visual or audio, word or non-word (VA WNW) discrimination task (3 8.5 min runs) and a paced breathing task with or without movie viewing (2-3 8 min runs). To evaluate the effect of component number on denoising and statistics, we fit the VA WNW task to the non-denoised data and created subject-specific, task relevant ROIs. Data was denoised using tedana with 20-200 components and the fit quality of the models were assessed via median Fisher Z scores, F statistics, and log(p-values). All methods' dimensionality estimates fell within a wide range (BSA: 21-81; LAP: 58-224) and all methods gave some implausibly low or high estimates. Within runs of data, estimates from different methods varied widely (estimates for one sample run: 31-95). CNR was positively associated with number of components in most task relevant ROIs. However, F statistics and log(p-values) were relatively stable as number of components increased, showing that statistics did not degrade despite loss of degrees of freedom. Overall, denoising quality was stable for component numbers between 20% and 50% of total timepoints, suggesting that any choice in this range is reasonable for the end user and won't significantly impact results. Ongoing efforts to optimize denoising explore tensor ICA (tICA), which uses all echoes to create components. tICA outputs an additional echo profile dimension which could inform inclusion criteria based on BOLD and non-BOLD signal decay profiles governed by MRI physics. While current tICA methods do not consider physical properties in component creation, our work-in-progress tICA algorithm optimizes for statistical independence (via an ICA-projection step) as well as physics informed echo profiles.

Disclosures: M.M. Smith: None. **D.A. Handwerker:** None. **K. Lam:** None. **J. Gonzalez-Castillo:** None. **F. Pereira:** None. **C. Walsh:** None. **T. Morgan:** None. **P. Bandettini:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.22/MM23

Topic: J.07. Data Analysis and Statistics

Title: Decoding Meditative States: A Longitudinal EEG and Psychological Questionnaires Dataset with Machine Learning Benchmark

Authors: A. LI[1], A. SYED[1], H. ALZWERI[2], T. LIU[3], B. H. COHEN[5], ***S. RAVISHANKAR**[1,4]; [1]Computat. Mathematics, Sci. and Engin., [2]Computer Sci. and Engin., [3]Psychology, [4]Biomed. Engin., Michigan State Univ., East Lansing, MI; [5]Applied Psychology, New York Univ., Greenwich, CT

Abstract: Continuous cognitive states like focused attention meditation (FAM) lack external triggers, complicating cross-subject and temporal neural decoding due to non-stationary drift and inter-individual variability. To address this, we introduce the Longitudinal Focused Attention Meditation Electroencephalography (L-FAME) dataset and benchmark. High-resolution 64-channel Electroencephalography (EEG) data and psychometric assessments were collected from 74 healthy college participants (46 females, 28 males, mean age: 22 years) randomized into three FAM techniques: Breath Focus (BF), Hare Krishna (HK) Japa (involves focusing on repeating the HK mantra), and SA-TA-NA-MA (SA) Japa. A subset of 44 individuals completed the full 6-week daily training intervention; attrition analysis validated a missing completely at random (MCAR) pattern. We evaluated machine learning and spatiotemporal deep learning models across three core tasks. Task 1 (Cognitive State Decoding) distinguished closed-eye rest (mind-wandering proxy) from silent meditation in EEG; deep learning achieved high intra-subject performance (EEGNet Area Under the Curve (AUC): 99.2% (mean) ± 2.1% (standard deviation)) but degraded severely during leave-one-subject-out (LOSO) cross-validation (66.6% ± 27.2%), with SA yielding the most generalized signatures. Task 2 (Technique Classification and Longitudinal Tracking) evaluated cross-subject identification of different meditation practices from EEG; classification Precision-Recall (PR)-AUC improved from pre-intervention (ShallowConvNet: 38.0% ± 6.2%) to post-intervention (EEGNet: 48.8% ± 8.6%), proving 6 weeks of training consolidated technique-specific neuroplastic signatures, with UMAP revealing clearer representational separation for somatic-based BF than phonological HK and SA. Task 3 (Cross-Session Generalization) evaluated whether decoding performance remains stable over the 6-week training gap despite natural temporal variations in EEG signals. Testing models (meditation vs. rest) from pre-intervention directly on the post-intervention session without updates caused AUC to drop from a 95.4% intra-subject ceiling to 63.1%, whereas a brief calibration using 30 samples recovered EEGNet AUC to 79.3%. Few-shot calibration highlights a scalable framework for continuous neurophysiological monitoring and longitudinal brain-

computer interfaces. The publicly available L-FAME dataset and benchmark establishes a novel, multi-session neural repository, offering a dedicated resource to track longitudinal neuroplastic changes induced by FAM training and evaluate model generalization over time.

Disclosures: A. Li: None. **A. Syed:** None. **H. Alzweri:** None. **T. Liu:** None. **B.H. Cohen:** None. **S. Ravishankar:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.23/MM24

Topic: J.07. Data Analysis and Statistics

Support: Rubicon grant 446-14-007 from NWO
Marie Sklodowska-Curie Global Fellowship 658868 from the European Union

Title: SMOOTH: A spatially principled framework for group-level inference in human intracranial EEG

Authors: *K. J. KHAN[1], B. GRAUL[2], A. STOLK[2];
[1]Penn MSTP, Philadelphia, PA; [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: Intracranial EEG (iEEG) provides unparalleled spatiotemporal access to human brain activity, yet principled group-level inference remains a major challenge because electrode coverage is sparse and anatomically uneven across individuals. This heterogeneity, together with the poorly characterized spatial dependence of task-evoked iEEG signals, has hindered the adaptation of spatially informed hypothesis testing procedures used widely in other neuroimaging modalities. As a result, iEEG studies typically rely on channel-level or atlas-based analyses, sacrificing either spatial precision or robust group-level inference, often at the cost of substantial multiple-comparison burden. Here, we show that task-related iEEG activity exhibits reliable spatial autocorrelation, demonstrating the need for null models that preserve local spatial structure to achieve valid cluster-level inference. We introduce SMOOTH, a statistical framework for group-level iEEG analysis that generates topographically constrained surrogate maps through spectral resampling. By decomposing subject-level cortical maps into orthogonal spatial frequency components and resampling their spectral coefficients, SMOOTH redistributes activity across the cortical surface while preserving intrinsic smoothness, yielding cluster null distributions for testing spatially consistent effects across individuals. Specificity analyses demonstrate that SMOOTH effectively controls family-wise error rate across increasingly smooth null fields, whereas spatially agnostic permutation approaches yield progressively inflated error rates as smoothness increases. Comparative analyses show that SMOOTH uncovers group-level effects not readily captured by conventional channel-level or atlas-based approaches. Relative to random sign flipping, a commonly used across-subject permutation strategy in M/EEG and fMRI, SMOOTH yields a deeper and more stable permutation ensemble

under uneven electrode coverage, improving sensitivity. Together, these results establish SMOOTH as a scalable, spatially principled framework for group-level inference in heterogeneous iEEG datasets, bridging the gap between spatial precision and robust population-level statistics while expanding opportunities for data-driven discovery in human intracranial neuroscience.

Disclosures: K.J. Khan: None. **B. Graul:** None. **A. Stolk:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.24/MM25

Topic: J.07. Data Analysis and Statistics

Title: Assessment of a mobile speech platformfor monitoring post-operative outcomes

Authors: *D. STARR[1], A. BURGESS[2], A. GUNDUZ[3];
[1]Univ. of Florida, Destin, FL; [3]Biomed. Engin., [2]Univ. of Florida, Gainesville, FL

Abstract: Deep brain stimulation (DBS) is an effective treatment for medication-refractory essential tremor (ET) by delivering electrical stimulation to targeted subcortical structures. ET is characterized by involuntary tremors that primarily affect the upper limbs, including the hands, arms, head, and voice. Since ET is a degenerative disorder, symptoms such as speech can significantly worsen with age. Additionally, long-term usage of continuous high-frequency can introduce off-target speech impairments or dysarthria. Currently, stimulation parameters (i.e., amplitude, frequency, etc.) are adjusted based on observable behavioral responses captured within the clinic, which unfortunately does not fully consider off-target impairment adjustments within a naturalistic environment. The objective of this study is to design, integrate, and evaluate an at-home mobile application to capture speech activity in a naturalistic environment. 30 research participants were recruited from the University of Florida to test the mobile application. The graphical user interface (GUI) was developed using the React Native Framework, which incorporates 4 gold standard tasks for assessing speech. Each participant underwent 2-3 trials, with qualitative and quantitative measures being recorded. Qualitative measures were gathered during pre- and post- trials, whereas quantitative measures represent the recordings gathered from the GUI. All trials were statistically analyzed at an individual and group level to determine the mobile applications' efficacy and efficiency. Results showcased that speech signal integrity can be efficiently collected, analyzed, and stored. Group-level analyses indicated areas of improvement within the GUI before implementation in a clinical environment. This work demonstrates a proof-of-concept GUI application to be incorporated within ET-DBS clinical programming.

Disclosures: D. Starr: None. **A. Burgess:** None. **A. Gunduz:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.25/MM26

Topic: J.07. Data Analysis and Statistics

Title: Feature Extraction across Epilepsy subtypes using Epileptogenic zone fingerprint

Authors: *C. BELLY[1], T. AUNG[2];
[1]Neurol., [2]OSF Healthcare Illinois Neurol. Institute, Peoria, IL, USA, Peoria, IL

Abstract: Objective: To characterize Epilepsy subtype - Mesial (ME), Temporal (TE), Neocortical epilepsy (NE) using Epileptogenic zone fingerprint (EZF) feature extraction.
Introduction: Surgical outcomes in epilepsy are largely dependent on accurate resection of the epileptogenic zone (EZ). A major challenge in epilepsy surgery is identifying the EZ a priori, as it has traditionally been defined retrospectively by the regions whose removal results in seizure freedom. One of the key objectives of intracranial EEG (iEEG) is to localize the seizure onset zone (SOZ), which is considered a surrogate for the EZ. Consequently, identifying reliable iEEG biomarkers of EZ has become a central focus in the field. With the advent of machine learning techniques, the concept of an “EZ fingerprint” has emerged as a potential biomarker. In this study, we aimed to extract and compare EZ fingerprints across different types of epilepsy.
Methods: The retrospective study of 48 patients with 2 patients having 2 seizure types a total of 50 patients were analyzed. These patients underwent SEEG implantation and resection surgery with Engle 1A surgical outcomes used to understand the seizure feature of epilepsy subtypes. Each seizure is 40 seconds long, 20 seconds before and after seizure onset along with 40 seconds background which is at least 2 minutes before seizure. The preprocessing and feature extraction analysis were performed on Brainstorm and EZF pipeline. The feature extraction is performed across SOZ, predicted EZ defined by EZF regions and Resected zone (RZ) electrodes group. The three features extracted are pre-ictal spikes (PI), Fast activity (FA), and Suppression. For statistics the group differences were assessed using the Kruskal-Wallis test with pairwise Wilcoxon rank-sum comparisons and Bonferroni correction ($p < 0.0167$). Effect sizes were quantified using Cliff's delta (δ): negligible ($|\delta| < 0.10$), small (0.10-0.29), medium (0.30-0.49), and large (≥ 0.50).
Results: Fast activity, SOZ showed significant differences across subtypes. Within the PZ and SOZ regions, The NE showed larger banding area than ME ($\delta = 0.47$, medium) and longer duration ($\delta = 0.29$, small). The average frequencies of ME at TBE and TBS of seizure are lower compared to NE and TE ($\delta = 0.27$-0.50, small-to large effects). Similarly, FA mask frequency of ME are lower than NE and TE ($\delta = 0.34$-0.44, medium effects). In PEZ the frequencies showed statistical significance at TBS and TBE. With banding and duration showed modest significance. with NE showing larger area than TE ($\delta = 0.26$, small) and longer duration than ME ($\delta = 0.34$, medium) and ETLE ($\delta = 0.28$, small).

Disclosures: C. Belly: None. **T. Aung:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.26/MM27

Topic: J.07. Data Analysis and Statistics

Support: JSPS KAKENHI JP22K18419, JP24K15161, JP25H00451, JP25K24744
JST Moonshot R&D Grant No. JPMJMS2021

Title: Beyond Canonical EEG Microstates: An Energy Landscape Analysis Framework for Modeling Complex Neural Dynamics

Authors: *A. ANUBHAV[1,2], K. FUJIWARA[1,2];
[1]The Univ. of Tokyo, Tokyo, Japan; [2]Intl. Res. Ctr. for Neurointelligence, Tokyo, Japan

Abstract: Classical EEG microstate analysis fundamentally relies on clustering, exclusively restricting data to Global Field Power (GFP) peaks to manage high-dimensional state spaces. This practice oversimplifies the data by imposing rigid temporal smoothing, which discards the continuous transitional dynamics present in neural activity. Instead, we utilize Energy Landscape Analysis (ELA), a framework initially introduced for fMRI, to establish a formal thermodynamic definition of EEG microstates. While EEG topographies are traditionally constrained to K=4 or 5 templates, by fitting a Pairwise Maximum Entropy Model (pMEM), this framework reveals metastable brain states as naturally emergent local minima within the underlying energy landscape. In this context, neural activity is rigorously modeled as dynamic traversals through this landscape, with transitions between states occurring when specific energy barriers are overcome. Furthermore, by quantifying the number and depth of these accessible local minima, ELA provides a direct mechanistic metric of cognitive flexibility, in which a restricted state space mathematically captures pathological network rigidity. To validate the downstream utility, we compared classical descriptive features (empirical dwell times and transition rates) against their thermodynamic drivers (average system energy and the total repertoire of unique accessible basins) across Healthy Control (HC) and Major Depressive Disorder (MDD) cohorts. Notably, the ELA features demonstrated enhanced predictive power, resulting in a significant increase in the area under the curve (ΔAUC=+0.17). In conclusion, the proposed EEG-ELA framework successfully recovers a naturally richer, thermodynamically grounded repertoire of metastable states, moving beyond the restrictive, predefined cluster limits of classical analysis.

Disclosures: A. Anubhav: None. **K. Fujiwara:** None.

Poster

PSTR294: Data Analysis and Statistics: Human Data II

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR294.27/MM28

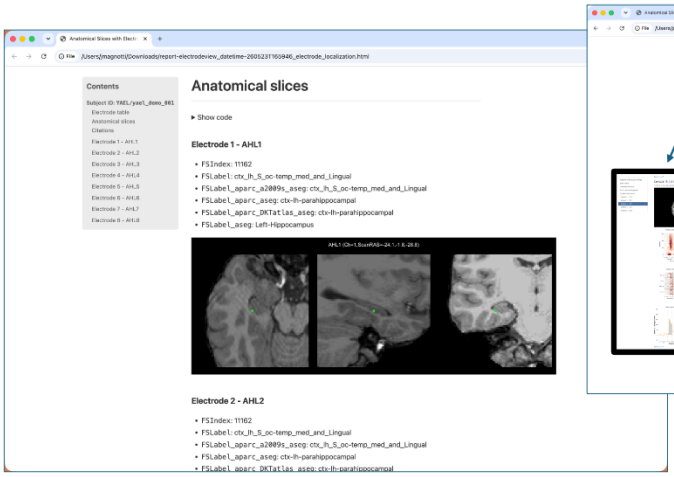
Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R01MH133717

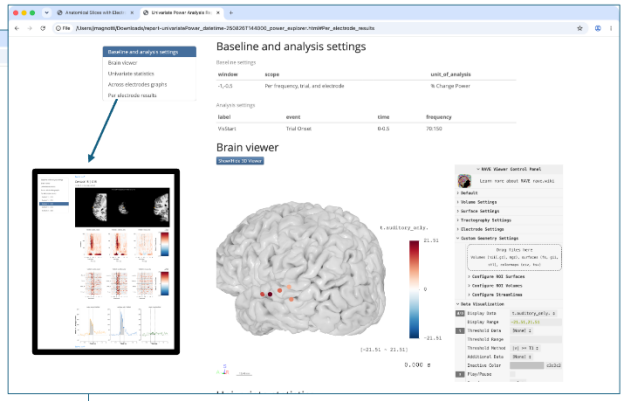
Title: RAVE Reports: Shareable, interactive summaries of human iEEG data at the single participant and group level

Authors: *Z. WANG, J. F. MAGNOTTI, X. ZHANG, M. BEAUCHAMP;
Dept. of Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: RAVE is a comprehensive software toolbox for iEEG analysis and visualization (https://rave.wiki). Because iEEG data are large and complex, with patient-specific imaging, locations for hundreds of electrodes, recordings from week-long hospital stays, analysis settings, and results of behavioral testing or tasks. This makes it difficult to share data and analysis between clinical and research teams and external collaborators. Researchers face a fundamental choice between sharing raw data (time-consuming and requires recipients to have specialized software and computational expertise) or sharing static results (limiting recipients to commenting on completed analyses rather than exploring the data themselves).
We developed a new workflow within RAVE, known as "RAVE Reports", that generates interconnected HTML files retaining the dynamic nature of raw data, including interactive 3D visualizations (Figure shows two sample reports). Individual reports provide self-contained representations of a single patient's data, while meta-reports can link across patients to represent case series or group analyses. To link multiple reports, RAVE Reports creates a static website that organizes and references individual reports (for instance, multiple participants in a study). RAVE Reports have three key advantages. First, they are ready-to-share files containing all critical patient- or group-level data, viewable in any web browser with no software installation. Second, report content is user-customizable through editing a plain-text file, with no programming required. Third, reports can embed RAVE's interactive 3D brain viewer, which supports a variety of surface, volume, and tabular data types, as well as drag-and-drop data addition, movie recording, and high-resolution image export for manuscripts. Shareable RAVE Reports provide access to diverse data types without requiring software installation. Broadly distributing data and tools enables more team members to contribute to scientific discovery.



Example localization report for 8 electrodes. Report includes slice view with electrode location highlighted (green point) and localization details from FreeSurfer



Example report looking at electrode-by-electrode functional activity. Report includes analysis meta data alongside interactive 3dViewer and several analyses per electrode (inset shows graphs for Electrode 15)

Disclosures: Z. Wang: None. **J.F. Magnotti:** None. **X. Zhang:** None. **M. Beauchamp:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.01/MM29

Topic: J.08. Methods to Modulate Neural Activity

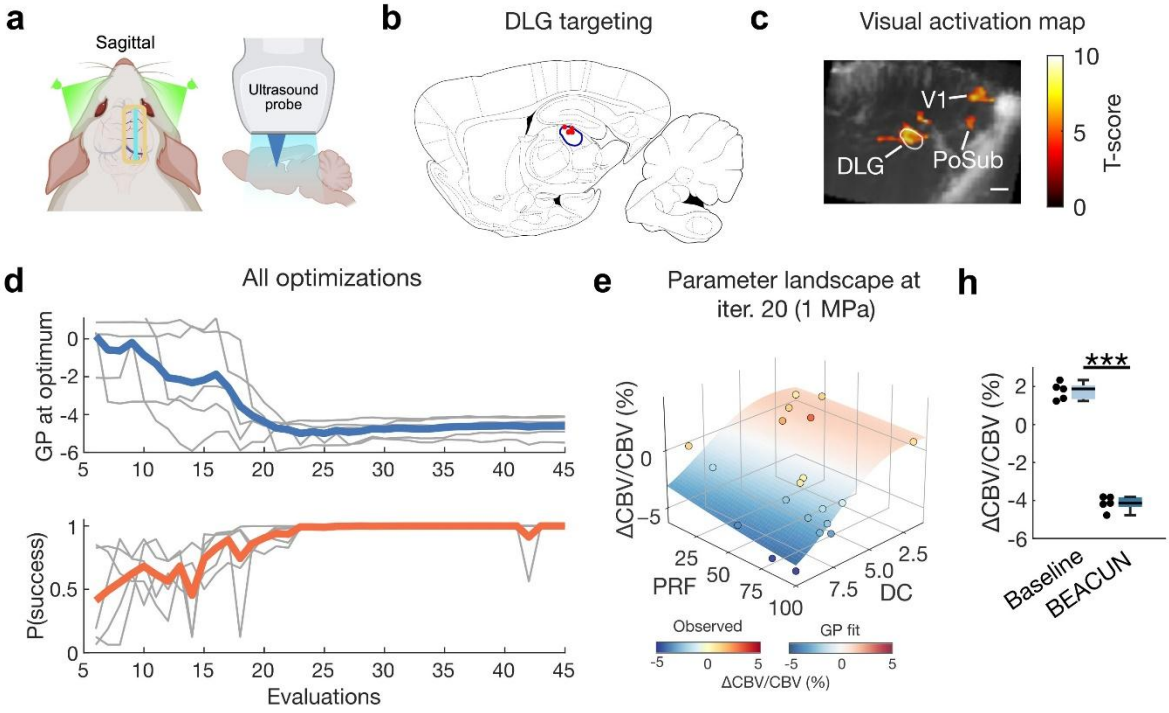
Support: National Institute of Biomedical Imaging and Bioengineering under grant 1R01EB036474
UCSF RAP Award
National Science Foundation NAIRR Pilot grant NAIRR250046
UCSF Catalyst Program and UCSF Weill Institute for Neurosciences

Title: Bayesian-enhanced closed-loop optimization of ultrasound protocols for targeted and precise neuromodulation

Authors: A. BOSCUTTI[1], V. GRASSO[2], *T. DI IANNI[3];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of California San Francisco, San Francisco, CA; [3]Psychiatry and Behavioral Sci., Univ. of California San Francisco, San Francicso, CA

Abstract: Low-intensity focused ultrasound (LIFU) is an emerging noninvasive neuromodulation technique that combines high spatiotemporal resolution with the ability to target deep brain structures. Despite its promise, the clinical efficacy of LIFU neuromodulation is challenged by a poorly understood parameter space and by high intra- and inter-subject

response variability. To address these challenges, here we developed and validated *in vivo* a platform for Bayesian-enhanced adaptive control of ultrasound neuromodulation (BEACUN). BEACUN enables efficient closed-loop parameter mapping using a limited number of stimulation-response evaluations.To validate the BEACUN approach for effective LIFU protocol optimization, we combined LIFU with functional ultrasound imaging (fUSI). After each LIFU stimulation, the evoked cerebral blood volume (CBV) signal at the target was quantified online and used to update a Gaussian-process surrogate of the stimulation-response function. The next stimulation parameters were then selected by the BEACUN acquisition function and updated at runtime in the fUSI-LIFU platform. We evaluated BEACUN in two inhibitory LIFU applications: one targeting the rat superior colliculus (SC; $N = 5$ rats), and a visual-evoked-response paradigm at the dorsal lateral geniculate nucleus (DLG; $N = 5$ rats) (**a-c**). In both experiments, pressure, pulse repetition frequency, and duty cycle were treated as continuous parameters (**e**). To enable fully automated optimization, we equipped BEACUN with a stopping criterion that halts the loop once a candidate point is deemed optimal.At the SC, BEACUN outperformed a real-world random search ($P < 0.01$; Hedge's $g = -4.24$) and produced a CBV signal reduction of -7.3% ± 1.19% (median ± IQR). At the DLG, BEACUN consistently suppressed the visual-evoked response (-5.7% ± 1% CBV reduction, $P < 0.001$, Hedge's $g = -12.68$) (**h**), and the stopping criterion halted the optimization after 23 ± 3.67 evaluations (**d**). These results establish BEACUN as an end-to-end closed-loop framework for data-driven, efficient LIFU parameter optimization *in vivo*.



Disclosures: A. Boscutti: None. **V. Grasso:** None. **T. Di Ianni:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.02/MM30

Topic: J.08. Methods to Modulate Neural Activity

Title: Functional ultrasound imaging-guided low-intensity focused ultrasound neuromodulation in a model of focal epilepsy

Authors: *V. GRASSO[1], J. KUM[1], Y. CHEN[1], T. DI IANNI[2];
[1]Univ. of California San Francisco, San Francisco, CA; [2]Univ. of California San Francisco, San Francicso, CA

Abstract: Low-intensity focused ultrasound (LIFU) is a promising neuromodulation modality, but the parameters required to induce reliable and robust neuromodulatory effects remain poorly characterized. Here, we combined functional ultrasound imaging (fUSI) and LIFU to enable ultrasound-based monitoring and modulation of neural activity within the same experimental framework and applied this approach in a rat model of focal epilepsy.
We first mapped the LIFU parameter space during visual stimulation in rats to identify effective neuromodulation protocols. We varied the pulse repetition frequency (PRF), the duty cycle (DC), and the acoustic pressure while targeting the superior colliculus (SC). LIFU protocols using a PRF of 100 Hz, a DC of 10%, and peak-negative pressure greater than 1 MPa effectively suppressed visual-evoked responses in the SC.
We then applied the optimized LIFU stimulation protocol in a rat model of focal epilepsy. We performed intrahippocampal injections of 4-aminopyridine (4-AP) to induce epileptiform activity. LIFU stimulation of the hippocampus effectively reduced the frequency of ictal events in treated (n = 3) vs. control rats (n = 3), as measured by fUSI and concurrent EEG recordings.

Disclosures: V. Grasso: None. **J. Kum:** None. **Y. Chen:** None. **T. Di Ianni:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.03/MM31

Topic: J.08. Methods to Modulate Neural Activity

Support: SZBL startup funding
Natural Science Foundation of Guangdong Province (Nos. 2023A1515010649)

Title: Ultrasound Distinctly Modulates Astrocytic and Neuronal Calcium Dynamics in a State-Dependent Manner in Mouse S1 Cortex

Authors: *F. LI;
Shenzhen Bay Lab., Shenzhen, China

Abstract: Ultrasound Distinctly Modulates Astrocytic and Neuronal Calcium Dynamics in a State-Dependent Manner in Mouse S1 Cortex
Astrocytes are abundant in the brain and their calcium signaling is reported to have an important effect on neuronal activity in both physiological and pathological conditions. Low-frequency focused ultrasound (FUS) has recently emerged as a powerful noninvasive neuromodulation approach, yet its impact on astrocyte calcium dynamics in different brain states *in vivo* is poorly understood. Here we combined a customized 0.521MHz FUS transducer with two-photon microscopy, allowing simultaneous single-cell resolution imaging and FUS stimulation at intensities of 0.91 or 1.5 W/cm^2 to examine astrocyte and neuronal calcium responses in somatosensory cortex of both awake and lightly anesthetized mice. In awake mice, FUS significantly enhanced the amplitude, frequency, and temporal integral of astrocyte calcium transients, while suppressing neuronal calcium activity and reducing the proportion of activated neuronal subpopulations. In contrast, lightly anesthetized mice displayed a blunted yet increased astrocyte response and negligible neuronal modulation under FUS, suggesting that baseline suppression from anesthesia partially masks FUS effects. Our study demonstrates that FUS elicits distinctive, state-dependent effects on cortical astrocytes and neurons, highlighting astrocytes as previously underappreciated targets of ultrasound neuromodulation. We further investigated the underlying mechanisms through pharmacological treatment and genetic manipulation. These findings will pave the way for FUS-based therapies targeting astrocyte–neuron interactions in conditions involving abnormal brain excitability.

Disclosures: F. Li: None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.04/MM32

Topic: J.08. Methods to Modulate Neural Activity

Support: Raynor Cerebellum Project

Title: Contrast-Enhanced Ultrasound Neuromodulation: A Histological Safety Assessment in the Mouse Brain

Authors: *M. GERLACH[1,2], R. M. JONES-SINNOTT[2], M. E. HEMELT[2], Y. DONG[2], O. V. FAVOROV[2], P. DAYTON[2], A. W. HANTMAN[3], G. PINTON[2];
[1]Emory Univ., Atlanta, GA; [2]Biomed. Engin., Univ. of North Carolina at Chapel Hill and North Carolina State Univ., Chapel Hill, NC; [3]Cell Biol. and Physiology, Neurosci. Ctr., Univ. of North Carolina at Chapel Hill, Raynor Cerebellum Project, Chapel Hill, NC

Abstract: Transcranial focused ultrasound (tFUS) is an emerging noninvasive neuromodulation technique capable of targeting deep brain structures with high spatial and temporal precision (100 μm, 1 ms). Combined with functional ultrasound imaging (fUSI) using circulating microbubble (MB) contrast agents, tFUS offers the potential for image-guided, closed-loop neuromodulation. However, because the biological effects of neuromodulation in the presence of MBs remain largely unknown, establishing the histological safety of contrast-enhanced tFUS is critical for broader application. Here, we assessed the histological effects of contrast-enhanced tFUS neuromodulation in awake mice across a range of free-field pressures, duty cycles (DC), and sonication durations (SD). Awake head-fixed mice received tFUS targeting the left primary motor cortex (M1; 1.77 mm lateral, 0.7 mm anterior to bregma) using a 1 MHz spherical transducer with an imaging aperture (Philips TIPS; PRF = 1000 Hz). Intravenous MBs were administered, and concurrent volumetric fUSI was performed using a 1024-channel Verasonics Vantage 3D system with a Vermon 32x32 matrix array (7.81 MHz, 500 volumes/s, 5-angle plane wave). Exposure conditions included free-field pressures of 180-300 kPa (40 kPa increments), DCs of 25-75% (pulse length 0.25-0.75 ms), and SDs between 4.5-54 s. Mice were euthanized 2 days after treatment. Brain sections (30 μm) were stained with hematoxylin and eosin (H&E) to assess structural damage and Fluoro-Jade C (FJC) to detect neuronal degeneration. Histological outcomes depended on the combination of pressure, DC, and SD. At 300 kPa and 72 stimulation cycles (1 s pulse train, 4 s inter-train interval (ITI) per cycle), damage occurred at 25% and 50% DC (corresponding SD = 18 s and 36 s, respectively). However, at 36 stimulation cycles, damage was only seen at 50% DC (SD = 18 s). At an intermediate exposure level (260 kPa, 75% DC, 36 stimulation cycles; SD = 27 s), injury occurred in 50% of mice, whereas no damage was detected at lower pressures or at 260 kPa with reduced DC. Comparison of histological stains revealed that FJC detected a greater extent of injury than H&E, identifying neuronal degeneration in regions with no H&E abnormalities. These findings indicate that MB-enhanced tFUS safety is governed by the combined effects of pressure, duty cycle, and sonication duration. Additionally, FJC is more sensitive than H&E for detecting subtle ultrasound-induced injury, supporting the need for complementary histological assessments. Overall, these results help define safer parameter spaces for MB-enhanced tFUS and support comprehensive histological evaluation of safety limits.

Disclosures: M. Gerlach: None. **R.M. Jones-Sinnott:** None. **M.E. Hemelt:** None. **Y. Dong:** None. **O.V. Favorov:** None. **P. Dayton:** None. **A.W. Hantman:** None. **G. Pinton:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.05/MM33

Topic: J.08. Methods to Modulate Neural Activity

Support: Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP27510389)

Nazarbayev University Grant No. 040225FD4718
KIST Institutional Program (Project No. 2E33771)

Title: Focused ultrasound shapes cortical network activity through excitability modulation and sensory input

Authors: *A. SARIEV[1], H. BAEK[2], D. JUNG[3], H. KIM[4], A. PAK[5];
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Abstract: Transcranial focused ultrasound (tFUS) enables non-invasive modulation of deep brain structures with high spatial precision; however, the mechanisms underlying its neural effects remain controversial. While some studies suggest direct modulation of neuronal activity, others attribute ultrasound-evoked responses to activation of auditory pathways.To distinguish between these possibilities, we compared cortical responses evoked by tFUS targeting either the lateral cerebellar nucleus (LCN), a major node of the dentato-thalamo-cortical (DTC) pathway, or the auditory cortex (AUD) in anesthetized rats. Electroencephalographic recordings were obtained from bilateral motor cortices and the contralateral auditory cortex. Event-related potentials (ERPs), spectral power, and inter-trial phase coherence were analyzed to assess pathway-specific network engagement.Both LCN and AUD stimulation produced robust responses in the auditory cortex, consistent with activation of auditory pathways. However, only LCN stimulation evoked early ERPs, enhanced gamma-band activity, and increased phase locking in the contralateral motor cortex. In contrast, AUD stimulation produced weak and bilaterally symmetric motor cortical responses. To interpret these findings, we developed a generative computational model comparing direct activation, sensory-driven activation, and a combined sensory-modulatory mechanism. Simulations showed that neither direct nor sensory-driven models alone reproduced the observed response patterns. Instead, a model in which sensory input provides the primary drive while ultrasound locally modulates neuronal excitability accounted for both widespread auditory activation and pathway-specific motor cortex recruitment.These findings support a dual mechanism of ultrasound neuromodulation in which sensory inputs drive large-scale cortical activation while local ultrasound effects bias the excitability of targeted circuits. This framework reconciles previously conflicting reports and provides insight into how focused ultrasound can selectively engage brain networks despite substantial sensory contributions

Disclosures: A. Sariev: None. **H. Baek:** None. **D. Jung:** None. **H. Kim:** None. **A. Pak:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

Time: Tuesday, November 17, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR295.06/MM34

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01GM103894

Title: Cortex and subcortex obey distinct parameter-effect rules in human focused ultrasound neuromodulation

Authors: *H. JANG[1,2], K. S. MEKA[1], A. YANG[1], Z. HUANG[1,2,3,4];
[1]Ctr. for Consciousness Sci., [2]Dept. of Anesthesiol., [3]Neurosci. Grad. Program, [4]Michigan Psychedelic Ctr., Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Transcranial low-intensity focused ultrasound (LIFU) noninvasively modulates human brain circuits and reaches subcortical targets beyond the depth of electromagnetic methods. Translation is limited by unpredictable outcome polarity. Nominally identical protocols facilitate neural activity in some studies and suppress it in others. Whether one parameter set acts uniformly across targets, or whether cortex and subcortex follow separate rules, has not been tested systematically. We synthesized 230 human LIFU experiments from 135 publications spanning 2014 to May 2026. Each experiment was coded for target, outcome polarity (facilitatory, suppressive, or null), and acoustic parameters, then positioned in a pulse repetition frequency (PRF) by duty cycle (DC) space using Gaussian kernel density estimation. Cortical and subcortical outcomes formed a double dissociation. PRF significantly predicted cortical polarity while DC governed subcortical polarity, and each parameter stayed uninformative in the opposite compartment. The cortical landscape was nonlinear, favoring facilitation at low-PRF/low-DC and at high-PRF/high-DC, suppression across intermediate values, and null outcomes at high-PRF/low-DC. The subcortical landscape instead rose monotonically with DC, shifting from suppression toward facilitation. The two maps significantly reversed at the theta-burst protocols. We also could not find any acoustic dose metric generalizing across compartments. Only 48% of experiments with a directional outcome assessed effects beyond 24 hours, leaving effect persistence as a major gap in the field. Human LIFU therefore obeys target-specific parameter-effect rules rather than a universal dose-response law, and effective neuromodulation requires target-tailored protocols instead of parameter transfer across regions. We release SonoMap (sonomap.github.io), an open database of all coded experiments, to support evidence-guided study design.

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Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR295.07/MM35

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH 1T32DC016853
NIH T32GM148382

Title: Methods for Personalized Vibrotactile and Thermal Transcutaneous Auricular Vagus Nerve Stimulation

Authors: *D. WILSON[1,2], P. ZOSS[1], M. J. SHADER[1], S. STEINHUBL[1], M. P. WARD[1,2]; [1]Purdue Univ., West Lafayette, IN; [2]Sch. of Med., Indiana Univ., Indianapolis, IN

Abstract: Electrical transcutaneous auricular vagus nerve stimulation (taVNS) is a promising neuromodulation strategy currently FDA-approved for migraine and opioid withdrawal management. However, its efficacy is highly variable and often limited by the pain thresholds associated with smaller fiber activation. The auricular branch of the vagus nerve (ABVN) is a somatic sensory nerve that provides inputs to the brainstem to elicit autonomic reflexes. Unlike electrical stimulation, which bypasses sensory endings to elicit axonal action potentials, thermal and vibrotactile stimuli may more naturally engage these endings. We developed a personalized, multimodal framework to explore the therapeutic potential of this natural recruitment. We developed a platform integrating high-resolution physiological monitoring with thermal and vibrotactile stimulation controlled via Python-Arduino protocols. Monitoring includes synchronized capture of electrocardiogram, electrogastrogram, electroencephalogram, galvanic skin response, continuous blood pressure, functional near-infrared spectroscopy, and pupillometry. The system utilizes custom 3D-printed ear-mounted apparatuses with a Peltier cell and a vibration motor designed to span the full dynamic range of ABVN sensations (10°C to 60°C; 10 to 220 Hz). A multiobjective Gaussian process regression algorithm was implemented in MATLAB to optimize parameters based on physiological biomarkers and subjective feedback captured via virtual reality-based surveys. Bench validation of the thermode demonstrated high precision (CV 2.36%±0.07%) and a mean absolute error of 0.69°C±0.02°C at target temperatures. Vibrotactile transducers maintained commanded frequencies with a mean absolute error 13.7 Hz±8.5 Hz across the 10-220 Hz range. Automated protocols successfully simulated parameter exploration for stimulus waveform optimization. The system has now been approved for human pilot testing by the Indiana Clinical and Translational Science Institute Scientific Review Committee and Purdue University IRB. Preliminary pilot data (n=14) indicates that vibrotactile stimulation at 200 Hz can elicit a 6.2% decrease in heart rate and a 20.7% increase in RMSSD. This multimodal platform provides a foundation for a noninvasive, closed-loop neuromodulation system. By optimizing parameters to reliably elicit physiological effects, such as heart rate lowering, in a comfortable or imperceptible manner, this approach enables a precision-medicine framework for developing effective predictable taVNS devices.

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Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR295.08/MM36

Topic: J.08. Methods to Modulate Neural Activity

Support: funded by a grant to WL from the focused ultrasound foundation

Title: Evaluation of low-intensity focused ultrasound neuromodulation of the anterior midcingulate cortex in patients with chronic pain

Authors: *A. KAPOOR[1], W. LEGON[2];
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Abstract: The anterior midcingulate cortex (aMCC) is a central component of pain-regulatory circuitry, integrating nociceptive, affective, and cognitive information while contributing to descending pain control. Its consistent dysregulation across chronic pain conditions makes it a compelling target for therapeutic neuromodulation. While single session LIFU can modulate deep brain function, it is unclear whether repeated aMCC stimulation can produce lasting changes in pain regulatory circuitry and sustained reductions in pain symptoms, which are critical requirements for clinical translation. Here, we tested the effect of repeated aMCC LIFU on patient-reported outcomes (PROMIS), heat-pain responses, EEG power, and fMRI resting-state connectivity. Twenty-two adults with chronic pain (16 female/6 male; 41.5±12.8 years) completed a single-blind, randomized, counterbalanced, within-subject crossover comparing aMCC LIFU with sham, separated by a 4-week washout. Each session delivered 8 40-s blocks (500 kHz, 30% duty cycle, 10 Hz PRF, 2.4 W/cm² Isppa at target) spaced 10 min apart. PROMIS Pain Intensity and Pain Interference were collected at baseline and at weeks 1-3. A subset (n=11) completed resting-state fMRI at baseline and 3 weeks after each condition. To investigate potential acute effects of LIFU on pain processing, we examined heat-pain thresholds, pain ratings to a heat stimulus and the EEG power response within session. Mixed models showed LIFU reduced PROMIS Pain Intensity versus sham (β=−3.50 T-score points, 95% CI [−5.43,−1.57], t(117)=−3.60, p<0.001), with maximal effects at 3 weeks. LIFU also reduced Pain Interference (β=−1.80 [−3.47,−0.13], p=0.030). Resting-state fMRI showed FDR-corrected decreases in aMCC connectivity with left dorsal anterior insula (z=−5.07), periaqueductal gray (z=−4.26), and bilateral thalamus (z=−4.12) 3 weeks after LIFU that may help explain sustained PROMIS effects. Acutely, LIFU reduced heat-pain intensity (β=−0.90 NRS, p=0.045) that was associated with reduced EEG frontal/central delta power. Repeated aMCC targeted LIFU produced sustained pain reductions and altered connectivity within pain related networks, providing initial evidence that repeated ultrasound neuromodulation may induce clinically meaningful and durable effects in chronic pain.

Disclosures: A. Kapoor: None. **W. Legon:** None.

Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR295.09/MM37

Topic: J.08. Methods to Modulate Neural Activity

Title: Relating Simulated Intracranial Pressure to Low-intensity Focused Ultrasound Neuromodulation Effects on Pain Perception

Authors: ***Y. NI**[1], S. GHOLIPOUR PICHA[1], W. LEGON[2];
[1]Virginia Tech., Roanoke, VA; [2]Fralin Biomed. Res. Inst., Roanoke, VA

Abstract: Low-intensity focused ultrasound (LIFU) is a noninvasive neuromodulation technique capable of reaching deep pain processing regions including the insula and cingulate cortices, yet how acoustic pressure at the target relates to the neuromodulatory effect on pain perception remains poorly characterized. Most studies apply a fixed extracranial pressure, but the pressure reaching the intended target varies across individuals due to heterogeneous skull morphology. Dose-response of LIFU is unknown and is critical to understand for future therapeutic applications. In this study, we performed a post-hoc modeling analysis from 73 different LIFU sessions (from two separate studies) targeting the anterior and posterior insula or anterior mid-cingulate cortex. Per session, intracranial pressure was simulated using individual MRI/CT. We extracted nine target-pressure and beam-focality features (e.g., peak and mean pressure at the target, inside-versus-outside focality ratios, and beam-target overlap) and related these features to the LIFU-induced behavior change (active vs. sham) in pain ratings. Each behavioral outcome was standardized (z-scored) within study so that positive values denote benefit (pain attenuation), that were then pooled across studies. We fit a linear mixed-effects model for each of nine pre-specified beam features spanning dose, focality, beam-target overlap, and spatial error separately, with a per-subject random intercept to account for repeated within-subject sessions and corrected across features using the false-discovery rate (FDR). Features capturing how well the beam concentrated on the intended target trended positively with behavioral benefit. Strongest was the inside/outside peak ratio, which is peak pressure inside the target ROI relative to outside, indexing focal selectivity ($\beta = 0.23$, $p = 0.071$), followed by FWHM beam-ROI overlap (Dice $\beta = 0.22$), and peak target pressure ($\beta = 0.18$). The pattern held analyzing independent studies separately (Study 1: peak ratio $\beta = 0.23$; Study 2 $\beta = 0.21$). No feature survived correction across the nine beam quantification metrics (all FDR $q > 0.30$), consistent with limited power from the small sample. These preliminary, directionally consistent results suggest delivered pressure and focality may contribute to LIFU efficacy, motivating larger datasets to test whether subject-specific delivered pressure can serve as a dosing parameter.

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Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR295.10/MM38

Topic: J.08. Methods to Modulate Neural Activity

Title: Human low-intensity focused ultrasound of anxiety and fear circuitry: target engagement and connectivity for threat responding

Authors: *S. GHOLIPOUR PICHA[1], W. LEGON[2];
[1]Virginia Tech., Roanoke, VA; [2]Fralin Biomed. Res. Inst., Roanoke, VA

Abstract: Low-intensity focused ultrasound (LIFU) is a noninvasive neuromodulation approach capable of selectively targeting deep brain regions. The right anterior insula (rAI) and anterior midcingulate cortex (aMCC) are key nodes in anxiety, fear, and threat-processing circuits. We tested whether LIFU targeting either region alters anxiety- and fear-potentiated responding during a threat task; whether acoustic target engagement predicts behavioral effects, and whether resting-state connectivity relates to stimulation responsiveness. Seventeen healthy volunteers completed three counterbalanced sessions: active LIFU targeting aMCC, active LIFU targeting rAI, and Sham. LIFU was delivered for 40 s at 10 Hz pulse repetition frequency and 30% duty cycle. After each session, participants completed the no-predictable-unpredictable (NPU) shock task, from which fear-potentiated responding (FPR) and anxiety-potentiated responding (APR) were derived. Target engagement was quantified as overlap between the brain region of interest and the subject-specific 50%, 71%, and 95% estimated LIFU beam-pressure volumes. Resting-state functional connectivity was estimated from 34 anxiety/fear-related regions and the six beam-derived regions (rAI and aMCC). Scan-level correlations were Fisher-z averaged. LIFU to rAI reduced both APR and FPR, while LIFU to aMCC reduced only FPR. LIFU-target overlap showed nominal behavioral associations, that included rAI 95% beam overlap with FPR effects ($r=0.51$, $p=0.025$). During Sham, FPR was negatively associated with secondary somatosensory cortex (S2)-aMCC connectivity ($r=-0.76$, $p=4.4e-4$). This association was numerically stronger after rAI LIFU ($r=-0.84$, $p=2.0e-5$, $q=0.016$). LIFU to aMCC and APR results showed no FDR-corrected associations with target engagement or functional connectivity. These findings demonstrate that LIFU can affect anxiety- and fear-potentiated responses during a threat task, however LIFU overlap with the intended target did not predict behavioral effects. Instead, rAI LIFU accentuated the negative relationship between somatosensory-cingulate connectivity and FPR, suggesting that intrinsic S2-aMCC connectivity may be an important circuit feature related to fear responding during rAI-targeted LIFU.

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Poster

PSTR295: Ultrasound Neuromodulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR295.11/Web Only

Topic: J.08. Methods to Modulate Neural Activity

Support: JSPS KAKENHI Grant Number 24K21318
JSPS KAKENHI Grant Number 23H03416

Title: Characterization of cortical neuronal responses to localized ultrasound stimulation using a piezoelectric micromachined transducer and dual-wavelength calcium imaging

Authors: *R. KITAHARA[1], T. YOSHIKAWA[1], T. TATENO[2];
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Abstract: Ultrasound stimulation (US) has emerged as a promising minimally invasive neuromodulation technique capable of targeting deep brain regions with high spatial precision. However, the underlying cellular mechanisms remain unclear, partly because US generates mechanical and optical artifacts that complicate in vitro functional measurements. To overcome these limitations at the cellular level, we developed an experimental platform integrating a piezoelectric micromachined ultrasound transducer (PMUT) with dual-wavelength calcium imaging in acute mouse auditory cortex slices expressing GCaMP7s. The PMUT enabled localized US delivery while preserving native circuit connectivity. To eliminate non-neuronal fluorescence fluctuations, calcium-dependent (460 nm excitation) and calcium-independent (405 nm excitation) signals were acquired alternately. Rather than employing conventional pseudo-ratiometric analysis, we estimated the linear relationship between the two channels using an affine transformation derived from least-squares fitting. This fitted model effectively corrected fluorescence artifacts unrelated to calcium dynamics, including photobleaching and motion artifacts induced by PMUT vibration, enabling stable extraction of neuronal calcium signals during US. While sham conditions (0-kPa) elicited no significant changes, robust fluorescence responses were detected during US. Characterization analyses revealed two major classes of temporal response patterns following US. In our previous framework, four response classes were identified; however, the affine transformation-based correction suppressed residual signal contamination, yielding more consistent and consolidated classifications. Alternatively, the relatively slow kinetics of GCaMP7s might still blur distinct temporal characteristics at response onset and decay. These results demonstrate that affine transformation-based artifact correction significantly improves the reliability of calcium imaging during US. Future studies employing GCaMP7f, which exhibits faster kinetics, will enhance temporal resolution to further elucidate the mechanisms of ultrasound neuromodulation.

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Poster

PSTR295: Ultrasound Neuromodulation

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Program #/Poster #: PSTR295.12/MM39

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH NS124564
NIH NS131069 (BH)

Title: Cell-Type-Specific Bidirectional Modulation of the Cortico-Thalamo-Cortical Sensory Pathway by Transcranial Focused Ultrasound

Authors: *H. GAO[1], S. RAMACHANDRAN[1], K. LEE[1], A. FRAKE[1], M. M. TORREGROSSA[3], B. HE[2];
[2]Dept. of Biomed. Engin., [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Transcranial focused ultrasound (tFUS) can noninvasively modulate sensory pathways, but the cell-type-specific mechanisms underlying excitatory or inhibitory effects remain unclear. In this study, we investigated how tFUS applied to the somatosensory cortex (S1) modulates cortico-thalamo-cortical (CTC) sensory pathway during hind paw vibration-tactile stimulation, and which neuronal populations mediate these effects. We applied a 128-element random array ultrasound transducer (H276, f_0 = 1.5 MHz) to stimulate S1 in anesthetized male rats (n = 34) and simultaneously recorded neural activity from S1 and posterior medial thalamic nucleus (POm). Vibration-tactile evoked potentials (TEPs) and multi-unit activity (MUA) were analyzed to assess sensory-evoked responses and their modulation by tFUS. Optogenetic tagging was used to identify S1 CaMKII-, PV-, and SST-positive neurons, while waveform features were used to classify putative excitatory (i.e., regular-spiking units - RSUs) and inhibitory neurons (i.e., fast-spiking units - FSUs) in POm. We found that only S1 CaMKII-positive neurons and POm RSUs responded robustly to tactile stimulation, whereas S1 PV-positive and SST-positive interneurons as well as POm FSUs showed minimal responses. tFUS applied to S1 produced strong parameter-dependent modulation of the CTC pathway. Stimulation with high pulse repetition frequency (PRF, 3kHz), high duty cycle (DC, 60%) and higher pressure (~163kPa) significantly enhanced tactile-evoked responses, indicating excitatory modulation of the sensory pathway. In contrast, stimulation with low PRF (30Hz), low DC (0.6%), and lower pressure (~98kPa) suppressed evoked responses, indicating inhibitory effects. Further analyses revealed that excitatory modulation was mediated by activation of S1 CaMKII-positive neurons, whereas inhibitory effects arose from their deactivation. These findings demonstrate that tFUS exerts bidirectional, parameter-dependent modulation of the CTC sensory pathway and highlight the critical role of CaMKII-positive neurons in mediating these effects. Importantly, these results have translational implications, suggesting that tFUS parameters can be optimized to either enhance or suppress sensory processing, providing a foundation for safe and effective tFUS-based therapies for sensory disorders.

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Poster

PSTR295: Ultrasound Neuromodulation

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH NS131069
NIH NS124564

Title: Modulation of reward cue-related neural activity and behavior in freely moving rats using low-intensity wearable transcranial focused ultrasound

Authors: ***M. KIM**[1], K. YU[2,1], E. HERRING[3], S. E. MORRISON[3], B. HE[1];
[1]Dept. of Biomed. Engin., Carnegie Mellon Univ., Pittsburgh, PA; [2]Biomed. Engin., Univ. of Connecticut, West Hartford, CT; [3]Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The nucleus accumbens (NAc) is a critical node linking neural activity to motivated behavior. Prior studies have demonstrated a relationship between cue-evoked excitation in the NAc and the latency to approach reward-associated targets. Given that reward-circuit dysfunction is a key feature of neuropsychiatric disorders, invasive neuromodulation has been used to target deep brain reward circuits such as the NAc; however, its clinical scalability is limited by the risks associated with surgical implantation. Therefore, there is a growing need for non-invasive approaches that can safely and effectively target deep brain structures. Low-intensity transcranial focused ultrasound (tFUS) is a promising non-invasive brain stimulation technology that combines high spatial precision with the ability to reach deep brain targets; however, its effects on neural activity and behavior during complex, task-engaged states in freely moving subjects remain poorly understood. In this study, we aimed to determine whether wearable tFUS can modulate reward cue-related behavior and neural activity in the NAc. Long-Evans rats were trained in a discriminative stimulus (DS) task, in which animals entered a magazine during presentation of an auditory cue to obtain a sucrose reward. A lightweight 64-element wearable random-array ultrasound transducer was developed and head-mounted, enabling freely moving behavior during stimulation. Then, a bilateral tFUS stimulation paradigm was combined with intracranial single-unit recordings. Each recording session pseudorandomly included approximately 25 tFUS trials, 25 negative control trials (transducer positioned identically, but no ultrasound delivered), and 25 non-discriminative stimulus trials (magazine entries had no programmed consequence). We found that tFUS targeting either the NAc or ventral tegmental area (VTA) using inhibitory parameters both attenuated cue-evoked neural activity in the NAc and increased latency to reward compared with the negative control condition. Furthermore, tFUS targeting the NAc using excitatory parameters reduced latency to reward compared with the negative control condition; however, the same parameters did not induce behavioral changes when targeting the VTA. Together, these findings demonstrate that tFUS can bidirectionally modulate cue reward-seeking neural activity and/or behavior in freely moving rats, highlighting its translational potential for neuropsychiatric disorders, including substance use disorders, eating disorders, and depression.

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