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Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.01/D1

Topic: A.06. Developmental Disorders

Support: DP1 NS142432

Title: Disrupted orofacial control during drinking in a mouse model of Rett syndrome

Authors: *A. D. FRIEDMAN[1], Y. KI[1], H. Y. ZOGHBI[2], N. LI[1];
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Abstract: Dysphagia is a prominent clinical feature of Rett syndrome (RTT) and can lead to food aspiration and pneumonia. However, the neural circuit mechanisms underlying impaired swallowing and aspiration risk remain poorly understood. Although impaired breathing–swallowing coordination is implicated in dysphagia in Rett syndrome (Ramirez et al., 2022), the contribution of tongue motor control deficits—and their underlying neural circuit mechanisms—have not been systematically examined. Clinical studies have reported oral-phase abnormalities in RTT, including hypo- and dys- kinetic tongue movements, prolonged oral transit, and poor bolus formation, suggesting that tongue dysfunction may contribute directly to dysphagia and aspiration risk (Morton et al., 1997; Motil et al., 1999; Abraham et al., 2015; Mezzedimi et al., 2017; Cocca et al., 2018). To define orofacial motor control during drinking, we developed a behavioral setup to measure licking, breathing, and swallowing in mice using high-speed videography, X-ray video fluoroscopy, and nasal airflow measurement. During drinking, mice collected water droplets from a waterspout through rapid rhythmic licking (~7 Hz), interspersed with intermittent swallows that cleared accumulated fluid from the oral cavity, while breathing continued in parallel across a broad range of frequencies. Using a mouse model of RTT that carries a *methyl-CpG-binding protein 2* (*Mecp2*)-null allele (*Mecp2*$^{+/-}$ RTT mice), we observed robust deficits in drinking behavior compared to age-matched wildtype controls. *Mecp2*$^{+/-}$ mice produced fewer licks, showed impaired targeting of the waterspout, and exhibited abnormal lick frequency. They also required more swallows to ingest a given volume of liquid and accumulated less water in the oral cavity before swallowing, suggesting impaired bolus formation. Swallow onset was less precisely coordinated with respiratory phase in *Mecp2*$^{+/-}$ mice, indicating disrupted swallow–breathing coordination. These deficits occurred alongside robust locomotor impairments, consistent with established motor phenotypes in RTT mouse models. This work establishes a behavioral framework for investigating the neural circuit mechanisms underlying tongue motor dysfunction and dysphagia in RTT.

Disclosures: A.D. Friedman: None. **Y. Ki:** None. **H.Y. Zoghbi:** None. **N. Li:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.02/D2

Topic: A.06. Developmental Disorders

Support: R01NS057819
P50 HD103555

Title: CRISPR screens identify CSNK2A1 as a druggable regulator of MeCP2 linking Rett and Okur-Chung neurodevelopmental syndromes

Authors: *A. ANDERSON[1], R. MEYER-SCHUMAN[1], E. CHU[2], H. Y. ZOGHBI[3];
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[3]Mol. and Human Genet., Baylor Col. of Medicine/HHMI, Houston, TX

Abstract: Precise regulation of methyl-CpG-binding protein 2 (MeCP2) is essential for normal neurological function. Loss-of-function mutations in *MECP2* lead to Rett syndrome (RTT), whereas duplication of the *MECP2* locus increases MeCP2 levels, causing *MECP2* duplication syndrome (MDS). Even modest (~30%) deviations in MeCP2 protein abundance produce neuropsychiatric phenotypes. Despite this sensitivity, the upstream mechanisms governing MeCP2 stability remain poorly understood. Using genome-wide CRISPR knockout screens, we identified casein kinase 2 alpha 1 (CSNK2A1) as a key regulator that directly binds and stabilizes MeCP2. A novel allosteric CSNK2A1 inhibitor reduced MeCP2 levels by ~35% in human cells, and genetic reduction of *Csnk2a1* rescued locomotor deficits and partially restored the disease transcriptional signature in a mouse model of MDS. We also found that CSNK2A1 influences the interaction between MeCP2 and chromatin-binding proteins implicated in RTT pathogenesis. Finally, we show that a missense lysine-to-arginine mutation at residue 198 (K198R) in *CSNK2A1*, the most common mutation found in Okur-Chung neurodevelopmental syndrome (OCNDS), reduces hippocampal MeCP2 levels by 45-50%, revealing convergent molecular mechanisms underlying both OCNDS and RTT. Together, these findings advance our understanding of how a dose-sensitive gene is post-translationally regulated and establish CSNK2A1 as a compelling therapeutic target for *MECP2*-related disorders.

Disclosures: A. Anderson: None. **R. Meyer-Schuman:** None. **E. Chu:** None. **H.Y. Zoghbi:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.03/D3

Topic: A.06. Developmental Disorders

Support: Lux Family Foundation

Title: A MECP2 mutation resulting in the deletion of Aspartic Acid 121 causes subnuclear mislocalization

Authors: *G. R. HARDY[1], S. S. BAJIKAR[2];
[1]Biomed. Engin., [2]Cell Biol. and Biomed. Engin., Univ. of Virginia, Charlottesville, VA

Abstract: Rett Syndrome (RTT) is a severe neurodevelopmental disorder affecting 1 in 10,000 live female births and caused by loss-of-function mutations in the methyl CpG-binding protein 2 (*MECP2*) gene. We are continually uncovering new variants of unknown significance (VUSs) in *MECP2*, but it remains unclear whether they affect MECP2 function and cause RTT in a given patient. Computational tools can help predict the pathogenicity of mutations; however, most tools are not designed to predict the impact of single-amino-acid deletions, making it challenging to assess these types of VUSs. Thus, functional validation of single-amino-acid deletion VUSs in *MECP2* is required. Recently, we identified a patient with developmental delay harboring a novel mutation resulting in the deletion of D121 (D121del). Missense mutations in D121 have been identified in ClinVar, with varying predicted impacts on MECP2 function. Whether deletion or mutation of D121 affects DNA binding and/or protein stability has not been extensively tested. D121 mediates R111 interaction with the GTG motif by stabilizing the methyl-binding domain with a salt bridge, which is required for binding to unmethylated DNA. Taken together, we hypothesize that mutations of D121, particularly its deletion, disrupt MECP2 function and cause RTT. We engineered model cell lines to overexpress D121del and D121 point mutations and analyzed MECP2 subnuclear localization and MECP2 stability. Preliminarily, deletion and most mutations of D121 drove abnormal MECP2 subnuclear localization and inconsistent colocalization with the nucleolus and heterochromatin marker H4K20me2/3. Additionally, D121 mutations did not alter overall MECP2 levels, suggesting a mechanism of mutation impact lies in MECP2 protein-DNA interactions rather than stability. We established a mouse model harboring a *MECP2* D121del mutation and have begun preliminary behavior studies. Future work will aim to expand on in vitro work in an immortalized neuronal progenitor line overexpressing MECP2 with the D121del mutation, study the effects of a single-amino acid deletion at D121 in the endogenous *MECP2* locus in a patient-derived iPSC neuronal model, and expand upon behavioral, transcriptomic, and DNA-binding experiments in vivo.

Disclosures: G.R. Hardy: None. **S.S. Bajikar:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.04/D4

Topic: A.06. Developmental Disorders

Support: R01 NS112171 to RG
F31 NS134246 to SG

Title: Heat Shock Factor 1 and Cellular Stress in Rett Syndrome Pathophysiology

Authors: *T. WILSTERMAN[1], S. GONZALEZ[2], M. STRATTON[3], L. LANE[2], R. GOGLIOTTI[2];
[1]Mol. Pharmacol. and Neurosci., Loyola Univ., Maywood, IL; [3]Mol. Pharmacol. & Neurosci., [2]Loyola Univ. Chicago, Maywood, IL

Abstract: Rett syndrome (RTT) is a neurodevelopmental disorder that is primarily caused by *de novo* loss-of-function mutations in the gene encoding the Methyl CPG Binding Protein 2 (MeCP2) protein. MeCP2 is a transcription factor that regulates the expression of thousands of genes, making it challenging to distinguish between those that are transcriptional noise relative to those that are pathogenic. While 95% of RTT cases arise from mutations in MeCP2, ~5% do not, resulting in a patient population termed MeCP2-mutation-negative, or atypical RTT. We hypothesized that comparing the transcriptome of typical and atypical RTT would be a viable way to reduce noise and identify conserved genes responsible for their shared clinical presentation. Differential RNA sequencing of temporal cortex autopsy samples from six typical, five atypical, and nine neurotypical controls identified that pathways associated with Heat-Shock Factor 1 (HSF1) signaling are dramatically elevated in both populations, a finding that was validated using a larger cohort of 40 RTT autopsy samples. HSF1 is a biosensor that coordinates transcriptional control of the cellular response to stress. To explore whether increased HSF1 signaling is compensatory or pathogenic, we conducted *in vivo* hyperthermia experiments alongside cellular stress array analyses. Preliminary data show both increased kinetics and magnitude of induction of cellular stress genes--attributable to increased transcriptional initiation and elongation rates. We further confirmed these results in a NSC model of RTT, spanning both severe and mild forms of the disorder. In vivo pharmacological data also aligned with hyperthermia experiments as induction of HSF1 evokes epileptiform activity in mouse models of RTT while inhibition rescues motor learning phenotypes and gut microbiome populations. We will present our most current findings on the role of MeCP2 and HSF1 in regulating the response to cellular stress in RTT.

Disclosures: T. Wilsterman: None. **S. Gonzalez:** None. **M. Stratton:** None. **L. Lane:** None. **R. Gogliotti:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.05/D5

Topic: A.06. Developmental Disorders

Support: Ovid Therapeutics
NIH NS087662
NIH NS081986
NIH NS108378
NIH NS101888
NIH NS103865
NIH R21NS126914
NIH R21NS111338
NIH R21NS111064
NIH MH118263
NIH MH097446

Title: Enhancing KCC2 Function with OV350 Reverses Neurological and Behavioral Phenotypes in Female MeCP2$^{+/-}$ Mice

Authors: *M. N. ARSHAD[1], T. NISHI[2], Z. ZHONG[2], P. A. DAVIES[3], S. J. MOSS[1]; [1]Neurosci., Tufts Univ., Boston, MA; [2]Ovid Therapeut., New York, NY; [3]Depatment of Neurosci., Tufts Univ. Sch. of Med., Boston, MA

Abstract: Rett syndrome is an X-linked neurodevelopmental disorder caused by mutations in the *MECP2* gene. It is characterized by intellectual disability, poor motor coordination, reduced social interaction, and seizures. A key feature of Rett syndrome is impaired synaptic inhibition resulting from weakened hyperpolarizing currents mediated by $GABA_A$ receptors. In mature neurons, effective inhibitory signaling requires low intracellular chloride levels, which are maintained by the neuron-specific potassium chloride cotransporter 2 (KCC2). During development, GABA signaling shifts from depolarizing to hyperpolarizing, a process dependent on KCC2 phosphorylation, which regulates its function and stability in the cell membrane. Disruption of KCC2 expression or phosphorylation has been linked to several neurodevelopmental disorders, including Rett syndrome. In this study, we investigated how the loss of MeCP2 affects KCC2 regulation in clinically relevant heterozygous MeCP2$^{+/-}$ female mice, which exhibit severe disease phenotypes. We found that MeCP2 deficiency significantly reduces KCC2 phosphorylation, thereby impairing transporter function. Electrophysiological recordings revealed increased baseline EEG power in MeCP2$^{+/-}$ female mice, indicating heightened network excitability, along with deficits in motor coordination, spatial memory, cognition, and sociability. To test a potential treatment strategy, we administered OV350, a novel small-molecule direct activator of KCC2 that enhances chloride extrusion. OV350 rapidly produced a sustained reduction in EEG power and decreased epileptiform activity. It also improved motor coordination, sociability, and spatial memory. Additionally, OV350 reduced the presence of activated (inflammatory) microglia. Importantly, OV350 did not alter overall KCC2 expression levels but restored its function by increasing phosphorylation at serine 940, a modification known to enhance transporter activity. Together, these findings demonstrate that impaired KCC2 phosphorylation contributes to network hyperexcitability and behavioral deficits in Rett syndrome. Thus, targeting KCC2 function may be a promising therapeutic approach for Rett syndrome and other neurodevelopmental disorders.

Disclosures: M.N. Arshad: None. **T. Nishi:** A. Employment/Salary (full or part-time):; Ovid Therapeutics. **Z. Zhong:** A. Employment/Salary (full or part-time):; Ovid Therapeutics. **P.A. Davies:** None. **S.J. Moss:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.06/D6

Topic: A.06. Developmental Disorders

Support: R61 NS144485
R21 HD111864

Title: Site-blocking antisense oligonucleotides: A solution to the Goldilocks-paradox in monogenic neurodevelopmental disorders

Authors: *L. LANE[1], A. M. VANDERPLOW[2], M. STRATTON[3], S. GONZALEZ[2], T. WILSTERMAN[4], Y. RHEE[5], R. GOGLIOTTI[2];
[2]Mol. Pharmacol. and Neurosci., [3]Mol. Pharmacol. & Neurosci., [1]Loyola Univ. Chicago, Maywood, IL; [4]Mol. Pharmacol. and Neurosci., Loyola Univ., Maywood, IL; [5]Northwestern Univ., Hinsdale, IL

Abstract: An emerging theme amongst monogenic neurodevelopmental disorders is a high degree of dosage sensitivity, such that both loss of function and overexpression are pathogenic. This narrow therapeutic window hinders gene therapy approaches because precise delivery of the appropriate dose must be achieved at a level that is often unique to cell type, brain region, and developmental stage. Methyl-CpG-binding protein 2 (*MECP2*) associated disorders represent this paradox, where loss-of-function mutations result in Rett syndrome (RTT) and a 1x overexpression leads to MeCP2 duplication syndrome (MDS). To address this therapeutic challenge, we have developed an antisense oligonucleotide (ASO) that targets microRNA (miRNA) to fine tune MeCP2 levels. miRNAs bind to pre-mRNA at the 3' untranslated region (3' UTR) to repress gene expression post-transcriptionally. Given that each miRNA's regulatory effect is modest and saturable, blocking miRNA binding may represent a therapeutic strategy for diseases with high dosage sensitivity. Site-blocking (sb) ASOs act by outcompeting repressive miRNA binding at the 3' UTR. This strategy aims to increase MeCP2 levels in patients with missense or late-truncating mutations, where the hypomorphic nature of the protein can be offset by enhanced abundance. Our results demonstrate that our lead sbASO, sb181, can elevate MeCP2 levels in a dose-dependent manner *in vitro* and *in vivo*, with MeCP2 plateauing at levels projected to be safe. Building on these results, we are expanding the sbASO strategy to other monogenic neurodevelopmental disorders that are highly dosage sensitive. One such disorder is caused by mutations in the chromodomain-helicase-DNA-binding protein 8 gene (*CHD8*), which is associated with atypical forms of RTT and whose regulatory network is linked to idiopathic autism. Like MeCP2, CHD8 is also highly dosage sensitive, with both over and under expression impacting neurodevelopment. There is also evidence of interaction between CHD8 and MeCP2 that suggests that they may be signaling partners. As disruption of the two genes results in overlapping phenotypes, it is possible that, in addition to overcoming primary mutations, the benefit of sbASO targeting of each one may have the potential to re-balance signaling associated

with loss of the other. This strategy would be most useful in the context of early-truncating or nonsense mutations, where the mutant protein is too unstable to be targeted. Here we present our most current data on the development of MeCP2 and CHD8 targeted sbASOs for the treatment of neurodevelopmental disorders. This study was funded by NIH awards R61 NS144485 and R21 HD111864 to RGG.

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Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.07/D7

Topic: A.06. Developmental Disorders

Support: International Rett Syndrome Foundation Innovator Award 2024

Title: Anxiety in a Rat Model of Rett Syndrome: A Longitudinal Approach

Authors: *M. KRAUTH[1], C. T. ENGINEER[2], C. K. MCINTYRE[2];
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Abstract: Rett Syndrome (RTT) is an X-linked neurodevelopmental disorder caused by mutations in the MECP2 gene. Affected girls appear to develop normally, then experience seizures and developmental regression with impaired motor, cognitive, sensory, and autonomic function. Heterozygous (Het) *Mecp2*$^{+/-}$ females from a transgenic rat model exhibit both mosaic MECP2 expression and skill regressions beginning at 5-7 months of age. While anxiety and sensory sensitivities are observed clinically, little data have been reported on these in Het rats. Furthermore, the relationship to underlying neural circuits is underexplored.
We are studying anxiety behavior via light-dark box and acoustic startle response (ASR) in female Het rats and wild-type (WT) littermates from ages 3 to 9 months. Additional anxiety and social tests conducted at 8/9 months include open field (OF), elevated plus maze, novelty-suppressed feeding, marble bury, wood chew, 3-chamber social interaction, and ultrasonic vocalizations.
ASR is robustly increased in Het rats across sound amplitudes (2-way ANOVA of genotype and amplitude genotype $p<0.0001$, amplitude $p<0.0001$, interaction $p=0.8230$ at 9 months), with no difference in pre-pulse inhibition. Differences emerge early in development (mean PTP voltage of 1.482 Het vs. 0.7563 WT, $p=0.0007$ at 5 months). Significant differences in light-dark box behavior are present beginning at 3 months and are more pronounced at higher light levels (average entries in light box 0.000 Het vs. 5.000 WT, $p=0.0058$ at 500 lux, 7 months). Hets spend less time in the center of the OF (2.567 sec Het vs. 25.850 sec WT, $p=0.0629$). Differences persist after adjusting for decreased locomotion of Hets. Social motivation appears unaffected,

consistent with the clinical phenotype.
Mecp2 het rats have stronger ASR, enter a light box less often, and spend less time in an OF compared to WT littermates. This profile suggests a difference in circuits governing baseline arousal and vigilance, exacerbated by sensory processing differences. These data support future studies exploring whether a novel treatment (vagus nerve stimulation) targeting autonomic dysfunction may help normalize circuit function and behavioral differences in RTT.

Disclosures: M. Krauth: None. **C.T. Engineer:** None. **C.K. McIntyre:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.08/D8

Topic: A.06. Developmental Disorders

Support: NIH Grant MH-118563-01 (LP-M)
Internal grant SGI-4232 (CA-T)

Title: Impaired Ensemble Synchrony in the Medial Prefrontal Cortex of Mecp2 KnockOut Mice During Social Conflict and Odor Recognition

Authors: *C. ACEVEDO-TRIANA[1,2], L. POZZO-MILLER[3];
[1]Univ. Pedagogica y Tecnologica de Colombia, Tunja, Colombia; [2]Sch. of Med., Univ. of Alabama at Birmingham, Birmingham, AL; [3]Pediatrics & Human Develop., Michigan State Univ., Grand Rapids, MI

Abstract: Neuronal activity in the mouse medial prefrontal cortex (mPFC) is closely associated with social behaviors and the encoding of social memories. In neurodevelopmental disorders such as Rett syndrome, these processes are often disrupted. Using Mecp2 knockout (KO) mice, a model for Rett syndrome, we investigated how altered mPFC ensemble activity might underlie deficits in social engagement and memory. We first confirmed reduced social dominance and engagement in male Mecp2 KO mice using two behavioral tests using genotype- and age-matched cage mate individuals: the traditional competition of the ‘tube test’ across 6 days tournament, and a novel ‘warm spot’ assay, in which three mice competed for a heated area in an arena with a cooled floor. Mecp2 KO mice displayed more submissive behaviors and lower social engagement compared to wild-type (WT) controls in both tests. To image intracellular Ca2+ signals as surrogates of neuronal spiking in vivo during the ‘warm spot’ test, we implanted a GRIN lens precoated with silk fibroin and AAVs to express the Ca2+ sensor GCaMP8 under control of the Camkii promoter in the prelimbic subregion of the mPFC. Mecp2 KO mice exhibited fewer and smaller Ca2+ transients and showed a reduced recruitment of socially-sensitive neurons during direct social interactions in the ‘warm spot’ test. Importantly, we found decreased synchrony among ensembles of co-active socially-responsive neurons in Mecp2 KO mice during key epochs of social interaction. To further examine neuronal responsiveness to

social stimuli under controlled conditions, a separate cohort of Mecp2 KO and WT mice were implanted with the same pre-coated GRIN lens along with a custom head-fixation device. During head-fixed imaging, we presented social odors using cotton swabs impregnated with urine from cage mates and a control non-social odor (vanilla) 30 times per day across all days of the tube test competition. Most mPFC pyramidal neurons in both genotypes exhibited selectivity for social odors, and a comparable number of co-active neuronal ensembles. Consistent with the 'warm spot' test, Mecp2 KO mice fewer active socially-responsive ensembles with a lower synchrony between them when compared to WT mice. Together, these results suggest that impaired social engagement in a mouse model for Rett syndrome is linked to disrupted temporal coordination among socially-sensitive pyramidal neurons in the mPFC.

Disclosures: C. Acevedo-Triana: None. **L. Pozzo-Miller:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.09/D9

Topic: A.06. Developmental Disorders

Support: NSF GRFP to Logan Dunn
NIH grant MH124042

Title: Dual-intensity whole-brain perineuronal net atlas reveals pervasive spatial and circuit level dysregulation in adult female mouse model of Rett syndrome

Authors: *K. KRISHNAN[1], L. DUNN[2], J. ELROD[3], J. MARTIN[4];
[1]Univ. of Tennessee At Knoxville, Knoxville, TN; [2]The Univ. of Tennessee - Knoxville, Knoxville, TN; [3]Biochemistry, Cell. and Mol. Biol., Univ. of Tennessee, Knoxville, TN; [4]Univ. of Tennessee, Knoxville, Knoxville, TN

Abstract: Perineuronal nets (PNNs) regulate neural circuit plasticity and are disrupted in neurodevelopmental disorders including Rett syndrome (RTT). Prior work has focused on high-intensity PNNs (hiPNNs) in restricted brain regions, leaving moderate-intensity PNNs (modPNNs) and whole-brain organizational principles uncharacterized. To address this, we performed comprehensive whole-brain mapping of hiPNN and modPNN expression across a pup retrieval behavioral timecourse in adult female Mecp2-heterozygous (Het) mice and wildtype (WT) controls (n=30 brains), generating a dual-intensity PNN atlas of the female mouse brain. Pup retrieval requires integration of auditory, olfactory, and tactile cues; Het females show inefficient retrieval, modeling the social communication deficits of RTT. PNNs were labeled via Wisteria floribunda agglutinin immunofluorescence across serial sections and quantified before, during, and after behavioral performance. We have published an IO protocol for mapping and registering the PNN atlas using QUINT. Anatomical region is the primary determinant of PNN density, explaining over 60% of variance. Het brains exhibit significantly elevated hiPNN and

modPNN density at every behavioral timepoint relative to WT. With repeated pup retrieval exposure, Het brains show disproportionately large decreases in PNN density concentrated in regions with established roles in sensory processing, spatial navigation, and maternal care. modPNNs emerge as a prevalent but previously uncharacterized subclass with distinct modulation across the behavioral timecourse. Spatial distribution analysis reveals disrupted PNN patterning in caudal Het brain regions, and machine learning classifiers trained on angular PNN distributions achieve above-chance genotype prediction, indicating spatially structured dysregulation. Interregional correlation analysis identifies a conserved network of brain regions that coordinately remodel PNNs across the WT behavioral timecourse; many are structurally connected via the Allen Brain Connectivity Atlas and implicated in maternal care circuitry. This coordinated remodeling is absent in Het brains. These findings demonstrate that PNN dysregulation in RTT is a brain-wide phenomenon with spatial and network-level organization. The WT dataset provides a foundational dual-intensity atlas of PNN expression in the female maternal brain. Het animals fail to appropriately modulate plasticity-regulating structures in regions relevant to their behavioral experience, implicating broad PNN dysregulation as a circuit-level mechanism underlying RTT behavioral deficits.

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Poster

PSTR080: Rett Syndrome and Down Syndrome

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Topic: A.06. Developmental Disorders

Support: NIH/NINDS grant R01NS931204
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Title: Dendrimer properties dictate the cell targeting, efficacy, and mechanism of action of ketamine in Rett syndrome

Authors: *P. VYAS[1], W. LIYANAGE[10], J. ALLENDE LABASTIDA[2], J. L. SOWERS[3], L.-R. SHAO[4], N. R. KALE[5], K. LAC[11], M. PAUL[12], M. P. AVALOS[6], K. MURUGESAN[7], C. E. STAFSTROM[8], K. PARIKH[9], R. KANNAN[1], S. KANNAN[13];
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Abstract: The nanoscale organization of therapeutic molecules can alter their receptor accessibility, cellular targeting, and biological activity independent of their chemical composition. We developed two non-releasing, functionally distinct, hydroxyl-terminated and glucose-dendrimer ketamine conjugates (HD-Ket and GD-Ket) and investigated how dendrimer conjugation reshapes the pharmacological effects of ketamine. Both conjugates are extensively characterized for their structure and stability, are highly soluble in saline, and serve as two pharmacologically distinct nanotherapeutic platforms. HD-Ket specifically targets activated microglia, and GD-Ket targets metabolically dysregulated neurons and glia that are primarily involved in disease pathology. Using a *Mecp2*-deficient mouse model of Rett syndrome (RTT), which recapitulates both glial and neuronal dysfunction, we demonstrate that dendrimer conjugation fundamentally changes the chemistry and pharmacology of ketamine. GD-Ket showed enhanced neuronal uptake and preferentially modulated neuronal N-methyl-D-aspartate receptor (NMDAR)-associated signaling pathways, thereby improving neuronal network synchronization and increasing expression of brain-derived neurotrophic factor (BDNF) and the synaptic scaffolding protein PSD-95. In contrast, HD-Ket preferentially targeted activated glial populations and more effectively suppressed neuroinflammatory responses in RTT. GD-Ket and HD-Ket conjugates showed differential intracellular localization across relevant cell types and pathological brain regions in RTT mice, while largely sparing healthy tissue, enabling cell-selective ketamine delivery. Systemic administration of both conjugates significantly improved survival and composite neurobehavioral, cognitive, and memory outcomes in *Mecp2-defici*ent mice, with greater efficacy than free ketamine. Both dendrimer conjugates retained functional activity while avoiding sedation, immobility, respiratory compromise, and the metabolic liabilities associated with free ketamine. Our findings demonstrate that cell-specific dendrimer-based targeting can dissociate the therapeutic benefits of ketamine from its dose-limiting toxicity, offering a promising, potentially safer approach to treating complex pathologies like RTT.

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options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Johns Hopkins.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.11/D11

Topic: A.06. Developmental Disorders

Title: Engineering ω-Based Hypercompact Base Editors for Efficient Correction of Rett Syndrome-Associated Mutations

Authors: *S. CICCONI[1], G. FENG[2];
[1]MIT, Boston, MA; [2]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Rett syndrome (RTT) is a neurodevelopmental disorder caused by pathogenic variants of the gene regulator MECP2, about 70% of which arise from single-nucleotide C-to-T mutations. The most severe forms of RTT commonly result from nonsense mutations in which a wild-type CGA codon is converted to the stop codon TGA, leading to premature protein truncation. Adenine base editors (ABEs), which convert adenines into guanines, present a promising therapeutic strategy through correction of the complementary adenine at the TGA nonsense site. Adeno-associated viruses (AAVs) are widely used for therapeutic gene delivery in the brain; however, their limited packaging capacity (<4.7 kb) restricts the use of conventional spCas9-based ABEs (>5 kb) for single-vector applications. To overcome this, we developed a compact ABE using ωIscB, a recently discovered Cas9 ancestor only 1.3 kb in size. We further engineered ωIscB through combinations of positively charged point mutations, modified DNA-binding domains (DBDs), and optimized guide architectures to enhance editing activity in human cells. The RTT-associated MECP2 R270X mutation was selected as a proof-of-concept target, and a fluorescent reporter system was established in HEK293T cells in which repair restored GFP expression. ABE constructs were fused with mCherry to confirm expression. Fluorescence-Activated Cell Sorting (FACS) was used to quantify the proportion of edited cells among editor-expressing cells. Editing activity and windows were further characterized at the endogenous A-rich VEGFA locus using PacBio sequencing to detect A-to-G conversions. Novel ωIscB ABEs were generated by combining multiple positively charged mutations with truncated and modified ωRNAs, alternative promoters, and reengineered DBDs. Constructs were benchmarked against a spCas9-based ABE reference editor. In total, 22 engineered ωIscB variants were developed and evaluated. Among the 22 constructs, editing efficiency increased from 0.5% in wild-type ωIscB to 20% relative to the spCas9 gold-standard ABE, representing a 40-fold improvement. The most efficient construct exhibited an editing window spanning positions A4-A6. The optimized ωIscB ABE measured 3.4 kb, substantially smaller than conventional spCas9 ABEs and well within AAV packaging constraints. These findings demonstrate that ωIscB is a viable platform for developing compact therapeutics to repair severe RTT mutations such as R270X in human cells. The small size, modularity, and improved editing activity of the engineered ωIscB ABE make it

a promising candidate for AAV-mediated gene therapy and support its potential for restoring MECP2 function.

Disclosures: S. Cicconi: None. **G. Feng:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.12/D12

Topic: A.06. Developmental Disorders

Support: (NIH) 1R01NS057819

Title: Dose-dependent molecular consequences of MeCP2 dysregulation in neurological disorders

Authors: *A. ENGSTROM[1], Y. LI[2], M. DIAS[1], A. ANDERSON[3], L. LAVERY[4], H. Y. ZOGHBI[5];
[1]Baylor Collage of Med., Houston, TX; [2]Mol. Human Genet., [3]Mol. and Human Genet., Baylor Col. of Med., Houston, TX; [4]Biosci., Rice Univ., Houston, TX; [5]Mol. and Human Genet., Baylor Col. of Medicine/HHMI, Houston, TX

Abstract: Methyl CpG binding protein 2 (MeCP2) binds methylated DNA to regulate transcription. MeCP2 is critical for neuronal function, and its levels are tightly regulated during postnatal mammalian brain development and in the mature brain. The brain is highly sensitive to MeCP2 dosage, with increased or decreased function leading to distinct neurological disorders, and the degree of change correlating with symptom severity. Mutations causing loss of MeCP2 function or reductions in its levels cause Rett syndrome, while milder mutations result in autism-like phenotypes. Conversely, duplication spanning *MECP2* causes *MECP2* Duplication Syndrome (MDS), and triplications lead to more severe symptoms and early lethality. Despite this established dosage sensitivity, the molecular consequences of varying MeCP2 levels in vivo are poorly understood. To address this, we leverage an allelic series of mouse models expressing a gradient of MeCP2 levels: 0% (null), 50% (hypomorphic), 100% (wild-type), 200% (MDS), and 350% (triplication). To identify how MeCP2 levels impact DNA-binding, the chromatin landscape, and gene expression, we performed CUT&RUN and RNA sequencing on the frontal cortex of these mice prior to symptom onset to capture molecular changes upstream of phenotypic deficits. CUT&RUN data show that MeCP2 binds broadly across the genome in all models, with a slight preference for promoters. When the protein is 50% of normal levels, MeCP2 binding decreases globally rather than at specific genomic regions or genes. Gene expression analyses demonstrate that reducing MeCP2 to 50% and 0% causes a dosage-dependent exacerbation of gene expression changes in both number and fold change magnitude. This correlation between MeCP2 levels, global binding, and gene expression extends to increased dosage models (200% and 350%). Analyzing gene expression changes across the

allelic series, we identify "dosage-dependent genes" dysregulated in a linear, progressive manner. These genes stratify into six clusters influenced by MeCP2 dosage and directionality of fold change, each with unique MeCP2 binding patterns that shift as levels change. Together, our data reveal that MeCP2 binding increases globally with dosage, but specific binding patterns across gene bodies are unique in dosage dependent transcriptional clusters. These changes occur prior to symptom onset, suggesting they are early molecular consequences of MeCP2 dosage alterations. This work advances understanding of the molecular basis of Rett syndrome and MDS and provides a framework for dissecting other dosage-sensitive genes.

Disclosures: A. Engstrom: None. **Y. Li:** None. **M. Dias:** None. **A. Anderson:** None. **L. Lavery:** None. **H.Y. Zoghbi:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.13/D13

Topic: A.06. Developmental Disorders

Support: NIH AG079002
NIH AG057468
NIH AG076940
NIH AG033570

Title: NORMALIZING APP DOSAGE RESCUES NEUROGENESIS AND ALZHEIMER'S DISEASE PATHOLOGY IN DOWN SYNDROME

Authors: *D. PATEL[1], K. RAKOWIECKI[2], O. LAZAROV[3];
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Abstract: Down Syndrome (DS) is the most abundant genetic form of mental retardation. It is caused by the triplication of partial or complete human chromosome 21 (HSA21). The molecular mechanisms causing it are not fully understood. Amyloid precursor protein (*APP*) resides on HSA21 and is triplicated in DS. APP plays a role in developmental and post-natal neurogenesis, but is not thought to be part of the Down Syndrome Critical Region (DSCR). The role of APP overdose in cortical malformation and cognitive impairments in DS is unknown. Mutations in *APP* cause familial Alzheimer's disease (FAD). However, whether APP overdose is sufficient for the development of Alzheimer's disease (AD) in DS is not fully understood. Here, we addressed the role of APP overdose in neuronal development and AD pathology. Using CRISPR-Cas9 gene editing, we knocked out one copy of *APP* from DS patient-derived induced iPSCs (DS APP+/+/-) and examined the effect on neurogenesis, AD-related pathology and the expression levels of genes on HSA21 that are implicated in DS, neurodegeneration and inflammation. APP triplication, in DS iPSCs, led to reduced stem cell proliferation, enhanced

differentiation into neurons, increased amyloid pathology, and altered protein levels of genes on HSA21. Correction of APP gene dosage restored proliferation, rescued altered neuronal differentiation and reduced pathological amyloidogenic processing. These data highlight APP dosage as a central driver of neuronal maturation and AD pathology in DS, suggesting therapeutic value in targeting APP expression to mitigate neurodevelopmental and neurodegenerative features of the disorder.

Disclosures: D. Patel: None. **K. Rakowiecki:** None. **O. Lazarov:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.14/D14

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

Title: Down Syndrome Associated Alzheimer's Disease Pathology in the TcMAC21 Down Syndrome Mouse Model

Authors: *D. SIKORSKI[1], S. KUMAR[2], K. HSIAO[3];
[1]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC; [2]Children's Natl., Washington DC, DC; [3]Children's Natl. Med. Ctr., Washington, DC

Abstract: Alzheimer’s disease (AD) occurs at a much higher rate in individuals with Down syndrome (DS), and the onset of AD along with its associated pathologies occur much earlier than in the euploid population. This risk is driven in part by triplication of the amyloid precursor protein (APP) gene on human chromosome 21, which accelerates amyloid accumulation, and is compounded by neuroinflammatory and cerebrovascular pathology. However, most existing DS mouse models lack expression of human APP, and therefore lack a critical component for modeling Down syndrome associated Alzheimer's disease (DS-AD). In our study, we used the TcMAC21 down syndrome mouse model, which contains an additional copy of human APP and other human chromosome 21 genes. To assess pathological progression in this model, brain samples were taken from TcMAC21 and B6D2 mice. For testing longitudinal pathological progression, each genotype was selected and sub-categorized by age into 5-6 week old young adults, 6-7 month old mature adults, and 1+ year old aged adults. Sagittal histology sections were then stained with ionized calcium-binding adaptor molecule 1 (Iba1) microglial marker. Quantification of microglial activation has typically been done via manual scoring, leading to unknown variability for the neuroinflammatory marker. To standardize the quantification process, we employed a deep learning software to classify the level of activation of each cell based on morphology and label it as one of six categorical sub-types. To test the blood-brain barrier structure, sections will also be stained with platelet endothelial cell adhesion molecule-1 (PECAM-1, CD31) and quantified for fluorescent area fraction using ImageJ processing software. These analyses establish a longitudinally resolved characterization of neuroinflammatory and cerebrovascular pathology in a genetically complete DS-AD model,

providing a framework for identifying mechanisms underlying accelerated neurodegeneration in Down syndrome.

Disclosures: D. Sikorski: None. **S. Kumar:** None. **K. Hsiao:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.15/D15

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

Support: Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) scholarship (22/12027-0 and 2024/04275–9)
Cell Sight Development Fund
Linda Crnic Institute for Down Syndrome
Research to Prevent Blindness.

Title: Human retinal histopathology reveals inflammatory and proteostatic remodeling in Down syndrome

Authors: *R. DA SILVA[1], E. JAMES[2], K. L. JONES-GRAHAM[3], M. HA[4], S. HAYDEN[6], A. HOWELL[7], S. PARWEEN[8], A. SAVIOLA[5], C. GIL[10], N. VERGARA[9];
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Abstract: Down syndrome (DS) is associated with increased retinal vulnerability and neurodegenerative alterations, yet the molecular mechanisms underlying retinal pathology remain poorly understood. This study aimed to elucidate the retinal alterations in Down syndrome and establish patient-derived retinal organoids as a translational platform for drug screening in DS-associated neurodegeneration. Post-mortem human trisomy 21 (T21) retinas and age-matched euploid control (D21) retinas were analyzed using proteomics and immunohistochemistry to evaluate inflammatory, glial, and proteostatic alterations. Patient-derivedT21 retinal organoids, together with euploid control retinal organoids, were generated for disease modeling and translational drug screening. Proteomic analysis revealed broad molecular remodeling in T21 retinas compared with D21 control retinas, including enrichment of inflammatory, extracellular matrix, ferroptosis, necroptosis, and NET formation pathways, togetherwith reduced expression of proteins associated with mitochondrial homeostasis, oxidative phosphorylation, and proteostasis. Immunohistochemical analyses demonstrated increased IBA1, GFAP, and IL-1β immunoreactivity in T21 retinas relative to D21 controls, consistent with retinal gliosis and inflammatory activation. T21 retinas also exhibited increased

phosphorylated tau (AT8 and T231), amyloid-associated markers (4G8 and 6E10), and NIAD-positive fibrillaraggregates compared with control retinas. Human T21 retinal organoids reproduced key pathological features observed in post-mortem tissue, including increased APP expression, phosphorylated tau accumulation, and amyloidogenicaggregates relative to euploid control organoids. To investigate therapeutic modulation, T21 retinal organoids were treated with the Annexin A1 mimetic peptide Ac2-26. Ac2-26 reduced phosphorylated tau, Aβ42, TNF-α, IL-17, IFN-α, andGFAP expression, while increasing neprilysin levels, suggesting enhanced amyloid clearance and attenuation of inflammatory signaling. Together, these findings identify the human DS retina as a site of chronic inflammatory and proteostatic dysregulation associated with AD-related pathology and establish retinal organoids as a translational platform for mechanistic studiesand therapeutic development in DS-associated neurodegeneration.

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Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.16/D16

Topic: A.06. Developmental Disorders

Support: NIH grant R01GM122463
NIH grant RF1AG057355
NIH grant R21OD032463

Title: Genes have expression ceilings that predict overexpression sensitivity

Authors: *J. T. PIERCE[1], S. SANCHEZ[2], S. IYER[1];
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Abstract: Many disorders are caused by the overexpression (OE) of genes, including cases of gene triplication (e.g. Down syndrome). An OE phenotype is believed to be caused when a gene's expression exceeds its maximally healthy threshold. Determining if and at what level a gene causes an OE phenotype remains challenging in part because most genes can be overexpressed without deleterious consequences, and OE thresholds across genes have been hypothesized but not seen. To identify a pattern of which genes cause OE phenotypes relevant to DS and at what levels, we studied OE for 47 orthologs of 21st chromosome genes in *C. elegans*. More than half caused developmental or behavioral deficits when overexpressed. Data mining revealed that most OE-sensitive genes showed ceilings of expression across wild *C. elegans* populations. This suggested natural selection against higher expression levels. Conversely, none of the OE-tolerant genes displayed expression ceilings. This model extended to independent worm studies and generalized to humans. We found that triplication-sensitive genes that cause

severe medical conditions display a ceiling of expression in a healthy population, e.g. *APP* - Alzheimer's disease, *PCSK9* - hypercholesterolemia, *PMP22* - Charcot-Marie-Tooth disease type 1A, and *SNCA* - Parkinson's disease. Likewise, when analyzing all human genes, we found that thousands of positive (or negative) control genes were more (or less) likely to have expression ceilings than chance. We developed a single-factor-based Truncation Index that quantified the degree of expression ceiling and found that it compared favorably with the 145-factor-based Triplosensitivity Index (from Collins et al. 2022) across all genes. We hypothesize that expression ceilings in *C. elegans* and human datasets represent OE thresholds above which cause an OE phenotype. To empirically test our quantitative hypothesis, we have begun testing if incremental changes in gene expression, above or below their predicted expression ceiling results in OE phenotypes in worm. Our model suggests that expression ceilings in healthy individuals predict if, and at what level, expression of a gene causes an OE phenotype. This framework may help discover genes that cause rare OE phenotypes and prioritize other genes to study in polygenic conditions such as DS.

Disclosures: J.T. Pierce: None. **S. Sanchez:** None. **S. Iyer:** None.

Poster

PSTR080: Rett Syndrome and Down Syndrome

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR080.17/D17

Topic: A.06. Developmental Disorders

Support: ZIA MH002982 and Valour Foundation

Title: State Dependence of Parvalbumin Autoantibodies in Down Syndrome

Authors: *P. R. PANDIT[1,2], D. OSPINA CARDONA[3], H. MAGER[5], A. ZOGHBI[6], A. SANDWEISS[7], J. D. SANTORO[8], C. M. BARTLEY[4];
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Abstract: State Dependence of Parvalbumin Autoantibodies in Down Syndrome
Priti R. Pandit, Ph.D [1], Daniela Ospina Cardona, B.S. [1], Anthony W. Zoghbi, M.D.[2], Christopher M. Bartley, M.D., Ph.D[1].[1] Translational Immunopsychiatry Unit, National Institute of Mental Health, National Institutes of Health, Bethesda, MD.
[2]Department of Molecular and Human Genetics and Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA
Abstract
Background: Down Syndrome (DS) is due to trisomy of chromosome 21, which encodes four of

six interferon receptors and the autoimmune regulator gene (AIRE). Elevated interferon signaling promotes a proinflammatory state, whereas paradoxical underexpression of AIRE likely contributes to the propensity toward autoimmunity in DS. We recently found that approximately 35% of individuals with DS harbor CSF-resident IgG class autoantibodies to parvalbumin (PVALB), a high-affinity cytosolic calcium (Ca^{2+})-binding protein expressed in fast-spiking GABAergic interneurons (PV-INs). PV-INs are less abundant in post-mortem brain tissue from DS and CSF PVALB levels are reduced in DS compared to healthy individuals or those with Alzheimer's disease. Because PVALB undergoes distinct conformational shifts upon calcium (Ca^{2+}) binding at its EF and CD hand domains, we investigated whether these specific binding properties are functionally relevant to PVALB-IgG recognition of PVALB.
Method: PVALB was C-terminally fused to nanoluciferase. Nanoluciferase immunoprecipitation system (nLIPS) was used to quantify the immunoreactivity of DS PVALB-IgG to PVALB in different cation-bound states by treating with EGTA or EDTA and rescuing with CaCl2 or MgCl2.
Results: EGTA (5 mM) and EDTA (10 mM) significantly reduced PVALB-IgG binding to PVALB as indicated by a >95% reduction in relative light units (RLU), indicating that chelation of divalent cations away from PVALB disrupts antibody recognition. Critically, adding excess MgCl2 (10 mM) or $CaCl_2$ (10 mM) to EDTA partially restored the RLU signal, confirming that PVALB-IgG preferentially binds to the Ca^{2+}/Mg^{2+}-bound state of PVALB.
Conclusion: These findings indicate that PVALB-IgG autoantibodies in DS preferentially bind to the divalent cation-bound state of PVALB—an observation with potential pathobiological implications. Future studies will introduce targeted mutations into the EF and CD loops of PVALB to evaluate their individual contributions to PVALB-IgG recognition.
Keywords : Down Syndrome Regression Disorder, Parvalbumin, chelators, neuroinflammation

Disclosures: P.R. Pandit: A. Employment/Salary (full or part-time):; Axle Informatics, which holds contract(s) with the National Institutes of Health. **D. Ospina Cardona:** A. Employment/Salary (full or part-time):; 22nd Century Technologies, Inc. holds contract(s) with the National Institutes of Health. **H. Mager:** A. Employment/Salary (full or part-time):; National Institutes of Health. **A. Zoghbi:** None. **A. Sandweiss:** None. **J.D. Santoro:** F. Consulting Fees (e.g., advisory boards); Dr. Santoro is a paid consultant for UCB, TG therapeutics, Dianthus pharmaceuticals, and Cycle Pharmaceuticals. **C.M. Bartley:** F. Consulting Fees (e.g., advisory boards); Dr. Bartley is an editorial board member at Biological Psychiatry and is a paid physician consultant for the Neuroimmune Foundation..

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.01/D18

Topic: A.07. Development of Neural Systems

Support: Croatian Science Foundation Grant No. IP-2022-10-8493 (Uniqueness in development of interneurons in human prefrontal cortex during fetal life and first

postnatal year—implications in pathogenesis of schizophrenia and autism, PI: Zdravko Petanjek)

Title: Protracted recruitment of immature neurons in the developing non-human primate telencephalon

Authors: *M. ČAVKA[1,2], M. ZANZE BEADER[1,2], Z. PETANJEK[1,2], A. HLADNIK[1,2], M. ESCLAPEZ[3];
[1]Croatian Inst. for Brain Res., [2]Dept. of Anat. and Clin. Anat., Univ. of Zagreb, Sch. of Med., Zagreb, Croatia; [3]INSERM, INMED, Inst. de Neurobiologie de la Méditerranée, Marseille, France

Abstract: Disruptions in cortical GABAergic networks are heavily implicated in neuropsychiatric disorders. In primates, the development of inhibitory circuits is remarkably protracted compared to rodents. Expanding on the evidence of extensive postnatal interneuron migration in humans, this study investigates the spatiotemporal migratory patterns of prospective GABAergic neurons in the macaque telencephalon across late prenatal and early postnatal stages from embryonic day (E) 127 to postnatal day (P) 12. Using immunohistochemistry for the immature neuronal marker doublecortin (DCX), we identified robust migratory streams persisting well into the perinatal period across multiple telencephalic regions. During late gestation (E127 and E147), dense, chain-like formations of DCX+ cells were prominent within the subventricular (SVZ) and intermediate zones (IZ), forming distinct regional streams that tracked along the walls of the lateral ventricle. We observed prominent corridors flanking the frontal, temporal, and occipital horns of the lateral ventricle. While substantially reduced in density by P12, these deep migratory streams remained detectable. To evaluate neurochemical maturation, we analyzed co-localization with the GABA-synthesizing enzyme GAD67, which was detected in a subset of DCX+ cells. Beyond migratory streams, we tracked a progressive redistribution of DCX+ cells into the cortical plate. While DCX+ cells were present throughout the full thickness of the cortical plate at E127 and E147, with a predominance in superficial layers, they became progressively restricted primarily to layer II by P12. These cells likely represent GABAergic neurons completing their radial dispersion into upper cortical targets. Our comparative findings suggest that the macaque telencephalon exhibits a protracted window for interneuron integration similar to that observed in humans. This provides an essential non-human primate framework that supports recent human findings while highlighting species-specific temporal dynamics in cortical development.

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Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.02/D19

Topic: A.07. Development of Neural Systems

Support: NIH Grant MH113257
Yale College First-Year Summer Research Fellowship in the Sciences and Engineering

Title: 3D anatomical reconstruction of the patch-matrix mosaic organization of the rhesus macaque striatum

Authors: *M. RODOV, P. RAKIC, A. DUQUE;
Neurosci., Yale Univ., New Haven, CT

Abstract: The striatum (ST) is a central component of the basal ganglia circuitry and plays a critical role in the dopaminergic regulation of motor and reward-related behaviors. Based on gross topography, the ST is divided into dorsal and ventral groups. The dorsal ST consists of the caudate nucleus (Cn) and putamen (Pu), which are separated by the internal capsule. The ventral ST includes the nucleus accumbens, the ventromedial extensions of the Cn-Pu, and a striatal portion of the olfactory tubercle (Gonzales and Smith, 2015). Along the rostro-caudal axis relative to the anterior commissure, the ST can also be divided into pre-commissural and post-commissural regions corresponding primarily to the head of the Cn and the body of the Pu. These anatomical subdivisions are functionally significant because they receive distinct, topographically organized projections from the cortex, thalamus, midbrain, and brainstem (Gabryel et al., 1978; Gerfen, 1984; Alexander et al., 1986; Voorn et al., 1989; Gonzales and Smith, 2015). The sole focus of this investigation is the reconstruction in 3D space of the complex compartmentalization of the ST, in the form of striosomes (patches) and surrounding matrix. This mosaic organization has been observed across multiple mammalian species and is associated with important differences in receptor expression, connectivity, and biochemical composition, including variations in cholinergic modulation from giant cholinergic interneurons (Parent and Hazrati, 1995; Bradfield et al., 2013). Despite extensive biochemical characterization of these compartments, a detailed anatomical reconstruction of their 3D organization remains incomplete (Mikula et al., 2009). Here, striosomal architecture was reconstructed from rhesus macaque striatal immunohistochemistry, notably calbindin and tyrosine hydroxylase sections spanning 70 days embryonic (E70) to adult (32.42 y/o). We selected brains with clearly defined patch-matrix boundaries and generated 3D meshes from high-resolution coronal images using consistent spatial calibration and alignment. Comparative analyses across hemispheres, sexes, and ages show that striosomal morphology is highly conserved, with strong structural similarity (overall ~97.89-98.81% via Hausdorff distance metric analysis) across matched regions. These findings provide a more complete anatomical framework for understanding how compartmental morphology and spatial organization relate to known biochemical and connectivity differences and support future work examining how these structures influence information flow within cortico-basal ganglia-thalamic circuits.

Disclosures: M. Rodov: None. **P. Rakic:** None. **A. Duque:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.03/D20

Topic: A.07. Development of Neural Systems

Support: Deutsche Forschungsgemeinschaft (DFG) - Projektnummer 512746157
Deutsche Forschungsgemeinschaft (DFG) - Projektnummer 514060831

Title: Decoding Transcriptiomal Programs That Generate Brainstem Neuronal Diversity

Authors: *F. MENG[1,2], Y. MOU[1,2], L. R. HERNANDEZ-MIRANDA[2,1];
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Abstract: Neuronal diversity in the brainstem is established during embryonic development through the coordinated action of transcription factors and their downstream regulatory programs. These developmental processes generate specialized neuronal populations that later participate in circuits controlling respiration, somatosensation, and motor behavior. However, the molecular principles that transform early developmental identities into mature, functionally distinct neuronal types remain poorly defined. To address this question, we investigated four molecularly distinct brainstem neuronal populations using an integrative framework combining single-cell transcriptomic, chromatin immunoprecipitation followed by sequencing, and computational reconstruction of gene-regulatory networks. This approach enabled us to follow neuronal identities across developmental stages and to identify the regulatory mechanisms associated with their specification and maturation. Our analyses uncovered population-specific transcriptional programs that progressively separate these neuronal lineages during development. Integration of gene-expression, chromatin-accessibility, and transcription-factor-binding information identified candidate regulatory interactions that link early lineage determinants to the acquisition of differentiated neuronal features. These datasets further allowed us to relate developmentally defined neuronal populations to mature brainstem cell types associated with somatosensory, respiratory, and motor circuits. Collectively, our results reveal how combinatorial transcription-factor activity organizes brainstem neuronal diversity across developmental time. They provide a molecular framework for understanding how embryonic gene-regulatory programs generate specialized neuronal populations and connect developmental origin with mature circuit identity. This framework may also help clarify how alterations in neuronal specification and differentiation contribute to disorders involving brainstem-dependent sensory, respiratory, or motor functions.

Disclosures: F. Meng: None. **Y. Mou:** None. **L.R. Hernandez-Miranda:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.04/D21

Topic: A.07. Development of Neural Systems

Support: NIH R01MH125479
NIH R01EB008374
NIH R01EB035160
NIH R01MH133836

Title: Female Brain Atlases Across the Human Lifespan

Authors: *S. AHMAD, K. HUYNH, G. LIN, P.-T. YAP;
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Abstract: Standardized brain atlases are central to developmental neuroscience yet remain predominantly sex-neutral or male-biased, despite well-documented sex differences in human brain structure and organization. Moreover, existing atlases mostly span adulthood, failing to account for lifespan brain changes. As a result, current approaches overlook the dynamic remodeling of the female brain across key endocrine transitions, including mini-puberty, adrenarche, menarche, pregnancy, and menopause. Female brain changes in response to hormonal modulation differ from those in males in magnitude, temporal dynamics, and regional distribution. Here, we introduce an unprecedented set of age-specific female brain atlases, densely sampled at 42 time points from birth to 100 years and derived from large-scale, multi-site MRI data pooled from dHCP, HBCD, BCP, HBN, HCPD, HCPYA, and HCPA studies. These MRIs were bias-field corrected and then uniformly processed with our age-agnostic brain tissue segmentation and cortical surface reconstruction method called NeuroVerse. The surface-volume atlases were jointly constructed using our hierarchical atlas construction framework. A set of reference templates was generated at select time points and standardized to a common space. Subject-specific MRI data were then spatially normalized to this common space using a surface-constrained deformable registration method (SCDEM). The resulting deformation fields were averaged and back-propagated to each time point to generate age-specific atlases comprising of T1-weighted and T2-weighted MRIs, tissue segmentation maps, and white and pial cortical surfaces. These atlases faithfully capture detailed anatomy with well-defined boundaries of the cortex, subcortex, and cerebellum. Dynamic changes in brain size are also accurately represented, including rapid expansion during infancy, continued growth through toddlerhood and childhood, and subsequent decline with aging. The cortical surface atlases characterize folding complexity across the lifespan, capturing gyral and sulcal patterns from coarse to fine scale. We validated geometric fidelity of our atlases by quantifying the error between atlas- and population-derived brain features (including volume and cortical thickness), demonstrating low discrepancies. A key strength of this resource is its consistency across both surface and volumetric domains, providing a unified reference framework for concurrent analysis of multi-domain brain features. It also establishes a normative reference for sex-informed neuroscience and enables more rigorous, unbiased studies of women's brain health.

Disclosures: S. Ahmad: None. **K. Huynh:** None. **G. Lin:** None. **P. Yap:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.05/D22

Topic: A.07. Development of Neural Systems

Title: Proteomic Characterization of Human Neural Progenitor Cells Reveals Matrix and Adhesion Changes Associated with the CHRFAM7AΔ2bp Variant

Authors: *N. ERICKSON[1], I. IHNATOVYCH[3], K. SZIGETI[4], N. KABBANI[2];
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Abstract: The CHRNA7 gene, located on chromosome 15q13.3, encodes the α7 nicotinic acetylcholine receptor (α7 nAChR) subunit and lies within a genomic region associated with multiple neuropsychiatric disorders. The human-specific fusion gene CHRFAM7A arose through duplication and rearrangement of CHRNA7 and FAM7A. While the direct CHRFAM7A allele negatively regulates α7 nAChR function, the inverted CHRFAM7AΔ2bp allele, which contains a two-base pair deletion in exon 6, has been linked to schizophrenia, bipolar disorder, and other psychiatric conditions. To investigate its molecular effects, we performed LC-ESI-MS/MS proteomic profiling on neuronal progenitors differentiated from isogenic human induced pluripotent stem cell (iPSC) lines carrying either the CHRFAM7AΔ2bp or CHRFAM7A-null genotype. Comparative analysis identified 129 differentially expressed proteins enriched in pathways related to extracellular matrix organization, collagen biosynthesis, and cell adhesion. Functional assays further revealed altered matrix adhesion in CHRFAM7AΔ2bp-derived progenitors, suggesting that this variant influences cellular architecture through modulation of adhesion and matrix-interaction proteins and may contribute to neuropsychiatric disease vulnerability.

Disclosures: N. Erickson: None. **I. Ihnatovych:** None. **K. Szigeti:** None. **N. Kabbani:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.06/E1

Topic: A.07. Development of Neural Systems

Title: Spatiotemporal Regulation of SMN1 and SMN2 Reveals Region-Specific Vulnerability Across Human Brain Development

Authors: *A. A. ALHAMDI[1], R. R. ALKHARJI[2];
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Abstract: Spinal muscular atrophy (SMA) is a neurodevelopmental motor neuron disorder caused by reduced survival motor neuron (SMN) protein, yet the spatiotemporal regulation of SMN1 and SMN2 across human brain development remains poorly defined. Emerging clinical, imaging and neuropathological evidence indicates that SMA also presents with brain-related phenotypes. This includes alterations in cortical structure, sensorimotor network connectivity and neurodevelopmental performance, highlighting the need to understand SMN gene regulation within the developing human brain. To address this, a comprehensive transcriptomic and genomic analysis of SMN1 and SMN2 were performed across prenatal and postnatal human brain development using multiple large-scale public datasets. Analysis of the Human Brain Reference Dataset revealed that both genes are expressed throughout prenatal development, with SMN1 consistently exhibited higher expression level than SMN2 across developing brain regions. Generalized additive models uncovered dynamic, non-linear developmental trajectories, with region-specific divergence suggesting differential SMN requirements across maturing neural circuits. Independent validation using the Allen Human Brain Atlas confirmed persistent expression of both genes from foetal to adult stages, with SMN1 remaining the predominantly expressed gene. The SMN2/SMN1 ratio varied markedly across regions and developmental periods, identifying potential windows of heightened neurodevelopmental vulnerability. Complementary genomic analyses characterized the distribution and predicted molecular impact of SMN1 variants, providing additional insight into population-level variability in SMN dosage. Together, these findings deliver the first lifespan-resolved, cross-dataset characterization of SMN1 and SMN2 expression in the human brain. The results reveal distinct temporal and regional expression patterns that may contribute to brain-related phenotypes in SMA and inform the timing and targeting of SMN-restoring therapies.

Disclosures: A.A. Alhamdi: None. **R.R. Alkharji:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.07/E2

Topic: A.02. Stem Cells and Reprogramming

Title: Regionally asynchronous development positions primary cortical folds in the human cortex

Authors: *L. LI[1], L. XU[2];
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Abstract: In humans, cortical folds emerge sequentially from early brain development through the neonatal stage. Although cortical folding is widely attributed to the amplification of outer radial glia (oRG), some primary cortical folds, such as the calcarine sulcus (CaS) and the cingulate sulcus (CgS), arise before the peak of oRG genesis. This suggests that alternative mechanisms govern the formation and spatiotemporal patterning of early-emerging cortical

folds. Here we show that developmental asynchrony generates regional variation in cortical cytoarchitecture and geometry, thereby specifying the positions of CaS and CgS. Our multi-omics analyses identify a genetic program in ventricular radial glia (vRG) that establishes developmental asynchrony across cortical regions. Our computational modeling further demonstrates that developmental asynchrony defines a mechanical instability locus, where growth-induced compressive stress preferentially accumulates to initiate sulcus formation. Together, our findings uncover a developmental-stage-dependent mechanism that governs the formation and spatiotemporal patterning of primary cortical folds in humans.

Disclosures: L. Li: None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.08/E3

Topic: A.07. Development of Neural Systems

Title: TCF4 Isoforms Coordinate Convergent and Divergent Molecular Programs During Human Forebrain Development

Authors: *R. C. SIMAMORA, F. BIREY;
Human Genet., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Isoform diversity significantly expands the functional repertoire of transcription factors, enabling precise and context-dependent regulation of brain development. Transcription factor 4 (TCF4) is a proneural basic helix-loop-helix (bHLH) transcription factor with an unusually diverse isoform repertoire and essential roles in forebrain development and function. TCF4 haploinsufficiency and sequence variants are strongly associated with neurodevelopmental disorders, including schizophrenia, epilepsy, intellectual disability, and Pitt-Hopkins syndrome, yet how individual isoforms contribute to human cortical development remains poorly understood. Defining how distinct TCF4 isoforms regulate developmental programs in a cell type- and stage-specific manner is therefore critical. Here, we leverage human forebrain organoid platform to map the spatiotemporal expression of TCF4 isoforms and define their molecular and cellular functions during human cortical development. Using bulk RNA sequencing across dorsal and ventral forebrain organoids, we show that TCF4 isoform dynamics are regionally and temporally regulated and recapitulate patterns observed in human fetal tissue. Long-read single-cell RNA sequencing combined with RNAscope further reveals that individual isoforms are enriched in distinct cell types across developmental stages, suggesting isoform-specific regulation of progenitor, neuronal, and interneuron-associated programs. To define function, we used CRISPR to selectively knock out TCF4-A or TCF4-B, the two predominant fetal brain isoforms, in human induced pluripotent stem cells and differentiated these lines into forebrain organoids. Transcriptomic and functional analyses of CRISPR-edited organoids uncover shared disruption of neuronal programs as well as isoform-specific effects on cortical developmental

trajectories. Together, these findings demonstrate that TCF4 isoforms are not functionally redundant but instead regulate overlapping and distinct programs across human forebrain development. By resolving TCF4 function at the isoform level, this work provides a framework for understanding how disease-associated variants in distinct regions of the gene may disrupt specific developmental stages, cell types, and molecular pathways, while informing future therapeutic strategies for TCF4-associated neurodevelopmental disorders.

Disclosures: R.C. Simamora: None. **F. Birey:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.09/E4

Topic: A.07. Development of Neural Systems

Support: NIAAA Grant R01AA030283
NSF award #2237795

Title: Maturation of Cognitive Control in the Inferior Frontal Junction: A Coordinate-Based fMRI Meta-Analysis

Authors: *C. MONTFORD[1], J. HOGEVEEN[2];
[1]Univ. of New Mexico, Albuquerque, NM; [2]Dept. of Psychology, The Univ. of New Mexico, Albuquerque, NM

Abstract: Cognitive control is thought to be made up of three domains: inhibition, switching or shifting, and working memory, which combine to support more complex executive functions. It is well documented that prefrontal regions undergo a protracted development, and it is hypothesized this neurobiological maturation leads to a similar trajectory in cognitive control. The inferior frontal junction (IFJ) is thought to play a domain-general role in supporting cognitive control processes, as evidenced by consistent activation during functional MRI tasks across cognitive control domains. The IFJ is functionally connected to different networks and has been shown to modulate the activity of other regions, supporting the notion that the IFJ is acts as a functional hub between networks. It is unclear, however, whether the IFJ's capacity for cognitive control enhances as a single construct, or if this region matures asynchronously for different control processes. To address this gap, the current work utilized neuroimaging meta-analyses to compare IFJ activation in youth (6-18 years) and adults (>18-45 years) across the three domains. Specifically, six Multi Kernel Density Analyses (MKDAs) were run to examine IFJ activation and co-activation patterns across domains, and three MKDA Chi^2 were run to compare the results in youth and adults. The final analyses were conducted with 18 studies in adults and 5 in youth for the inhibition analyses, 23 studies in adults and 2 in youth for the switching analyses, and 17 studies in adults and 6 in youth for the working memory analyses. Consistent convergence of activation was found in the IFJ across domains in adults, while in

youth the IFJ only exhibited convergence during tasks of inhibition, suggesting inhibition may be a developmentally foundational process localized to this region earlier in the lifespan. The current results highlight the importance of the IFJ in cognitive control, and support a model where this region does not mature as a monolithic node, but instead acts as a dynamic hub that integrates fractionated cognitive processes at different developmental stages. The findings are also indicative of a gap in the literature, as there are only two studies in youth that that met inclusion criteria for the analysis of switching studies; future studies in this area are warranted.

Disclosures: C. Montford: None. **J. Hogeveen:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.10/E5

Topic: A.07. Development of Neural Systems

Support: NIH R01 MH128745
NIH R21 MH125367
UPMC CMRF

Title: Persistent Postnatal Structural Plasticity in the Human Entorhinal Cortex

Authors: *S. R. JETT[1], L. O. VAASJO[2], S. KOTERMANSKI[1], M. A. NASCIMENTO[5], T. J. ABEL[3], S. CHAMBERLAND[4], S. F. SORRELLS[4];
[2]Neurobio., [3]Dept. of Neurolog. Surgery, [4]Dept. of Neurosci., [1]Univ. of Pittsburgh, Pittsburgh, PA; [5]Inst. of Biophysics, Federal Univ. of Rio De Janeiro/Ufrj, Rio DE Janeiro, Brazil

Abstract: The entorhinal cortex (EC) is a key structure in the brain responsible for episodic memory. While much of the human brain is built embryonically, the human EC continues to develop after birth. We previously found a unique stream of migrating interneurons continuing to arrive in the human EC up to 1-2 years postnatally, with no similar postnatal contribution in the macaque. The majority of these late-arriving neurons were derived from the caudal ganglionic eminence (CGE), a population of interneurons that typically reside in the most superficial layers of the brain and control incoming signals onto excitatory neurons. To further explore the development of the postnatal human EC, we immunostained postmortem brain samples for markers expressed by immature cells and interneurons. Our immunostains revealed columns of immature cells with migratory morphology oriented toward superficial layers of EC at early postnatal ages, with clusters of doublecortin (DCX) and polysialylated neural cell adhesion molecule (PSA-NCAM) positive neurons in layer II enveloped by dense LAMP5+ fibers emanating from layer I. We then used label transfer from the Allen Institute's human Patch-seq dataset onto our existing dataset which revealed significant diversity in the CGE-derived interneuron subtypes within the EC including subtypes reported in the human brain with no known equivalent in the rodent. Analysis of differentially expressed genes (DEGs) between the

late-arriving interneurons suggests a divergence of functional roles between cell types. We then investigated how dynamic superficial layer cells in human EC are using acute slice electrophysiology and time-lapse confocal microscopy from surgically resected pediatric EC samples (N=6 donors, 11 months - 19 years). Morphoelectric properties in EC interneurons revealed greater heterogeneity than predicted by label transfer on our RNA-sequencing data, suggesting either unique regional or developmental contributions. Viral labeling and time-lapse imaging in adjacent brain slices showed highly dynamic structural plasticity in superficial layer cells, with extensive neurite remodeling and soma translocation even in young adult brains. Overall, our results suggest that cells in superficial layer EC exhibit persistent structural plasticity which may contribute to the enhanced memory capabilities in humans.

Disclosures: S.R. Jett: None. **L.O. Vaasjo:** None. **S. Kotermanski:** None. **M.A. Nascimento:** None. **T.J. Abel:** None. **S. Chamberland:** None. **S.F. Sorrells:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.11/E6

Topic: A.07. Development of Neural Systems

Support: NSF-GRFP DGE 2139839

Title: Age and Sex Differences in Neural Responsivity to Peer Acceptance and Rejection in Early Childhood

Authors: *M. REDIC;
Psychological and Brain Sci., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Preschool- and elementary-aged children spend significantly more time with peers than infants and toddlers, making this a salient period to study early neural responses to social feedback. The present study aimed to measure differences in children's neural activity (i.e., EEG frequency bands) to peer acceptance versus rejection and determine whether age and sex were associated with responsivity. Children aged 4 to 7 years old (n=173; Mean age (SD) = 6.26 (1.06) years) completed the playdate task and received feedback about whether peers wanted to play with them (acceptance) versus not play with them (rejection), with trials randomized across the task. Time frequency analyses isolated and averaged 5000ms windows during accept and reject conditions at electrode Fz. T-statistic topographic maps were created to identify and extract data from regions of interest (5ms of significant condition differences, recorded at 1000Hz sampling rate) and multitaper phase locking was used. Across children, responsivity differences to condition were observed in gamma and late alpha-beta frequency bands (greater responsivity to acceptance; p's < .02) as well as in delta-theta, delta, theta, and early alpha-beta frequency bands (greater responsivity to rejection; p's < .003). In moderator analyses, older children showed greater responsivity in alpha-beta, delta-theta, and late alpha-beta frequency

bands to both types of feedback (p's < .001). Older children also had greater responsivity in delta and theta bands and greater differences based on feedback type (with larger response to rejection; p's < .001). When examining sex moderations, girls had greater overall delta, theta, and delta-theta responsivity than boys across both conditions (p's < .02). Compared to boys who had similar responsivity across conditions in early alpha-beta bands, girls had much greater responsivity to rejection than acceptance (p = 0.02). Conversely, boys had a greater responsivity difference in gamma frequency bands, with a larger response to acceptance, compared to girls (p = 0.03). Taken together, findings indicate that, responsivity to rejection is greater at most frequency bands compared with acceptance, and there are age- and sex-related differences, with older children and girls exhibiting greater responsivity to feedback. Findings indicate that neural response peer rejection is increasingly salient in girls and as children enter school-age in early childhood. Future work should examine social functioning and psychiatric predictors of responsivity differences.

Disclosures: M. Redic: None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.12/E7

Topic: A.07. Development of Neural Systems

Support: NSF grants 1640909 (JJV)
NSF 1735095 (CM)
DOE P200A240132 (CM)

Title: Study of Neurodevelopmental disorder Participants' Movement Data Using surface Electromyographic, and Kinematic sensors plus Artificial Intelligence Techniques

Authors: C. MCKEEVER[1], K. DOCTOR[2], W. TRASK[3], *J. V. JOSE[1];
[1]Indiana Univ., Bloomington, IN; [2]Universiity of Massachusetts, Amherst, Mumbai, India;
[3]Indiana Univ. Bloomington, Bloomington, IN

Abstract: It is widely recognized that neurodevelopmental disorders (NDD) are a major health problem in the US. CDC statistics indicates that there are 1/36 children with autism spectrum disorder (ASD), 9.4%, with Attention-Deficit/Hyperactivity Disorder (ADHD), and about 70% of ASD are comorbid with ADHD. There are not sufficient providers, however, to diagnose all needing participants in a timely manner. In a recent paper we studied the data produced by NDD participants carrying out the reaching protocol (1). Using Deep Learning techniques, we could promptly assess NDD conditions. We also analyzed the millisecond statistical kinematic magnitude fluctuations giving quantitative estimate of the severity of each NDD participant. However, these results are phenomenological in nature. They do not provide deeper biological information or a deeper understanding of why each NDD or NT participant has unique kinematic

features. To address this question, we have added surface electromyography (EMG) sensors working together with the kinematic sensors. We carried out the same reaching protocol for each NDD and NT conditions as before. We tested a new cohort of ASD, ADHD, ASD+ADHD plus NT participants. As in (1) the Deep Learning analysis for the EMG and kinematic joint data sets was carried out with the unfiltered data. For the analysis of the kinematic and EMG data we filtered out the electronic noise present in the sensors. We needed to simultaneously correlate the EMG and the kinematic filtered data sets, which operate at different time scales. Thus, carried out careful filtering of the data, following established practice in the EMG community. We will discuss the differences found in EMG measurements for different NDD and NT conditions for the unfiltered and filtered data sets and describe their correlations.

Disclosures: C. McKeever: None. **K. Doctor:** None. **W. Trask:** None. **J.V. Jose:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.13/E8

Topic: A.07. Development of Neural Systems

Support: R01HD114489

Title: Dense Longitudinal Neuroimaging Reveals Individualized Trajectories for Visual Word Processing Across the First-Grade Year

Authors: *X. REN[1,3], J. R. BOOTH[4], G. AMOROSINO[5], F. PESTILLI[6], K. N. KAY[7], S. VINCI-BOOHER[2];
[2]Psychology and Human Develop., [1]Univ. of Notre Dame, Notre Dame, IN; [4]Dept. of Psychology and Human Develop., [3]Vanderbilt Univ., Nashville, TN; [6]Psychology, [5]The Univ. of Texas at Austin, Austin, TX; [7]Radiology, Univ. of Minnesota, Twin Cities, St Paul, MN

Abstract: Learning to read transforms the developing brain, with the visual word form area (VWFA) emerging as a critical cortical region for word processing. Prior work has demonstrated that the VWFA is anatomically well-positioned to support visual word form processing during reading acquisition; here, we investigated the emergence of decodable VWFA responses as first-grade children learn to read using monthly dense longitudinal neuroimaging (DLN). We collected task-based fMRI data and measures of reading performance from nine children each month throughout their first-grade year, including baseline and endline scans (108 datasets total). We localized the VWFA in each child at their endline scan using a standard category localizer and extracted fMRI responses to images from a naturalistic visual stimulus dataset (Sesame Street) at each scan across the first-grade year. To assess selectivity for visual word processing, we quantified the decodability of four categories in the child-specific VWFAs across the first-grade year: words, digits, faces, and places. First, all children progressed from below- to above-average reading scores (standardized) from the beginning to the end of the first-grade year.

Second, the onset of decodable information in the VWFA varied across children, suggesting individual differences in when the VWFA begins to process visual word forms. Finally, decodability in the VWFA was not stable: within a given child, some monthly sessions yielded decodable information while others did not, indicating that the emergence of word-selectivity in the VWFA is non-linear. Together, these findings suggest that visual word processing in the VWFA may emerge along individualized, non-linear trajectories during early reading acquisition - varying in onset across children and fluctuating across months - rather than appearing at a single fixed point and persisting thereafter.

Disclosures: X. Ren: None. **J.R. Booth:** None. **G. Amorosino:** None. **F. Pestilli:** None. **K.N. Kay:** None. **S. Vinci-Booher:** None.

Poster

PSTR081: Mechanisms of Neurodevelopment: Humans and Non-Human Primates

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR081.14/F1

Topic: A.07. Development of Neural Systems

Title: Attention Guided Transfer Learning for Gestational Age Prediction from Fetal Brain MRI

Authors: M. ZUBAIR, E. PICCIRILLI, M. CAULO, ***C. DEL GRATTA**;
Gabriele D'Annunzio Univ. of Chieti and Pescara, Italy, Chieti, Italy

Abstract: Gestational age (GA) prediction is a crucial component of prenatal care, providing an objective basis for monitoring fetal brain development and identifying potential neurodevelopmental or pathological risks. Ultrasound is widely used for gestational age estimation, but image quality can be limited by fetal position, maternal body habitus, low amniotic fluid, and later gestational stages. Fetal MRI provides high-resolution anatomical information about the developing brain, but automated methods for extracting maturational markers are still to be validated.
We implemented an attention-guided multiplanar transfer learning framework to predict gestational age from fetal brain MRI. The dataset included 261 T2-weighted fetal MRI studies acquired at the Institute for Advanced Biomedical Technologies, Gabriele D'Annunzio University of Chieti and Pescara, Chieti, Italy, with axial, coronal, and sagittal planes. DICOM MRI slices were converted into 16-bit PNG files to preserve the full dynamic range and subtle signal variations without introducing compression artifacts. The images were then resized to 224 × 224 pixels and formatted as RGB three-channel inputs for a VGG16 model pre-trained on ImageNet. Key fetal brain slices were selected from each anatomical plane, and both single-plane and multi-plane configurations were evaluated. The classification layers of VGG16 were replaced with regression layers to estimate gestational age continuously. Attention mechanisms were incorporated to emphasize informative fetal brain regions and improve interpretability. Model performance was assessed using 5-fold cross-validation and evaluated with the coefficient of determination (R^2) and mean absolute error (MAE) in days.

Multi-plane models outperformed single-plane approaches, indicating that complementary anatomical views improve estimation of fetal brain maturation. The best model combined multi-plane fetal MRI with attention-guided transfer learning, achieving $R^2 = 0.9581$ and MAE = 4.51 days. Attention maps highlighted brain regions that contributed most strongly to the prediction, supporting the biological plausibility and interpretability of the model.
These findings suggest that attention-guided deep learning can extract clinically meaningful developmental information from fetal MRI and provide accurate gestational age prediction. This approach may support objective assessment of fetal brain maturation and contribute to future AI-based tools for prenatal neurodevelopmental evaluation.

Disclosures: M. Zubair: None. **E. Piccirilli:** None. **M. Caulo:** None. **C. Del Gratta:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.01/F2

Topic: A.07. Development of Neural Systems

Support: NSF CRCNS 2113028

Title: BECOMING AN ADULT: TUNING OF FORCE SENSING IN COCKROACHES IN THE FINAL STAGES OF DEVELOPMENT

Authors: *S. N. ZILL[1], **S. S. CHAUDHRY**[1], N. D. KATHMAN[2], N. S. SZCZECINSKI[3]; [1]J.C. Edwards Sch. Med., Huntington, WV; [2]Biol., Marshall Univ., Huntington, WV; [3]West Virginia Univ., Morgantown, WV

Abstract: Growth in animals is often a continuous process but with discrete acceleration in size and mass as juveniles become adults. The mechanisms that adjust the nervous system to this transition have not been specifically characterized. We have studied and modeled the morphology and response characteristics of force detecting sense organs (campaniform sensilla) in the legs of late stage juvenile and adult American cockroaches. In cockroaches, this transition involves a substantial increase in body mass from 650 mg (mean of pre-adult stage (10th instar of Gier, 1947) to 980 mg (males) or 1090 mg females in adults. There is also a concomitant increase in body size, reflected in the length of the hind leg tibia which grows from mean length of 9.8 mm to 12.2 mm (males and females). We are currently recording the responses of force receptors located in the hind leg tibia (campaniform sensilla) in late stage juvenile and adult animals to bending forces. These tests show a large increase in the range of forces encoded by the receptors. Studies of the morphology of the receptors have also shown that there is an increase in the size of the site of sensory transduction (cuticular caps) of the largest sensilla. We are also testing responses of receptors to forces applied at different positions on the tibia to evaluate the contributions of skeletal and neuronal properties to the changes in force sensing. These data indicate that the transition from juvenile to adult forms involves the synchronous

increase in both the forces generated by the animal and the sense organs that detect and monitor those forces.

Disclosures: S.N. Zill: None. **S.S. Chaudhry:** None. **N.D. Kathman:** None. **N.S. Szczecinski:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.02/F3

Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant GM158116
NIH Grant CA156734

Title: Minibrain controls neural stem cell birth in the Drosophila optic lobe

Authors: *J. ROSEN[1], G. ABEBE[2], A. VERAKSA[1];
[1]Univ. of Massachusetts Boston, Boston, MA; [2]Univ. of Massachusetts Boston, Melrose, MA

Abstract: Minibrain (Mnb) is a serine/threonine kinase that controls the development of the brain and other tissues in *Drosophila melanogaster*. Mutations in the *mnb* gene disrupt the wing, brain, gut, and cuticle of the fly and are also associated with severe behavioral defects. Mnb exerts its control over development via several established mechanisms, including interactions with the protein Capicua and with components of the Hippo pathway. Our preliminary data suggest a novel mechanism: namely, that Mnb is required for the proper birth of neural stem cells from their precursor tissue, the neuroepithelium. Most studies of Mnb focus on its role later in development, and to date, no study has established a role for Mnb in the context of neural stem cell birth. We propose to use a combination of immunohistochemistry, interactomics, and lineage tracing methods in vivo and in vitro to elucidate the role of Mnb in the birth of neural stem cells. So far, preliminary data suggests that Mnb may be affecting neural stem cell formation by controlling the activity of the Notch signaling pathway, by regulating intracellular trafficking decisions in the optic lobe, and by establishing cell polarity of neural stem cell precursors. Mnb's human ortholog, *DYRK1A*, located on chromosome 21, is involved in several diseases, including Down syndrome, cancer, Alzheimer's, and diabetes. Although DYRK1A has potential as a therapeutic drug target, most drugs that target DYRK1A are toxic and/or ineffective. By deepening our understanding of how Mnb impacts brain growth, we hope that our work may lead to better treatments for patients afflicted by DYRK1A-related diseases.

Disclosures: J. Rosen: None. **G. Abebe:** None. **A. Veraksa:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.03/F4

Topic: A.07. Development of Neural Systems

Support: NIH R15 HD110963-01

Title: Cell type specificity of vasopressin 1a receptor expression in developing mouse brain

Authors: *M. FURLONG[1], H. K. CALDWELL[2];
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Abstract: Arginine vasopressin (Avp) signaling through the Avp 1a receptor (Avpr1a) is involved in the sex-specific neural modulation of social behaviors in juvenile and adult animals. However, evidence suggests that Avpr1a signaling may also be involved in shaping sex-specific neural circuitry during embryonic development, ultimately impacting behavior over the lifespan. Work from our laboratory has already demonstrated that the Avpr1a is present and functional as early as embryonic day (E) 16.5. However, the cell types that express the Avpr1a remains unknown. Thus, in this study we set out to assess the expression of the Avpr1a in neurons and glia using RNAscope over embryonic and postnatal development. We hypothesized that the Avpr1a would be expressed in both cell types. We used timed pregnancies and collected tissue on E16.5, E18.5, postnatal day (P) 0, and P2. We then evaluated the colocalization of Avpr1a mRNA with a marker for neurons (NeuN) or glia (S100B). At this time the data analyses are ongoing but understanding the cell type specificity of Avpr1a expression will help determine the possible impacts of Avpr1a signaling during brain development and the mechanisms by which behavior might be affected.

Disclosures: M. Furlong: None. **H.K. Caldwell:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.04/F5

Topic: A.07. Development of Neural Systems

Title: Differential Activity of the Transcription Factor Nkx2.1 in Embryonic Mouse Brain, Lung, and Thyroid

Authors: *M. T. MANION;
NICHD, Bethesda, MD

Abstract: Individual transcription factors are often expressed in multiple cell and tissue types during development, but with distinct genomic targets. This in part explains why human variants in transcription factors can lead to complex, multi-organ phenotypes that are challenging to treat. Mechanisms that guide differential transcription factor activity in distinct tissues are not well understood. Possible mechanisms that guide transcription factor specificity are (1) tissue-specific chromatin accessibility, (2) tissue-specific co-factors and adaptor proteins, and/or (3) tissue-specific genomic binding motifs that recruit a specific set of transcription factors. The transcription factor Nkx2.1 is expressed in the embryonic thyroid, lung, hypothalamus, and medial ganglionic eminence (MGE), where it plays critical roles in development of these tissues. In the MGE, Nkx2.1 serves as a 'master regulator' for all MGE-derived GABAergic inhibitory neurons, while in the lung, it regulates differentiation of alveolar cell subtypes. Humans with NKX2.1 mutations suffer from the aptly named Brain-lung-thyroid syndrome and display neurodevelopmental symptoms, impaired respiration and hypothyroidism. Thus, Nkx2.1 represents an ideal candidate to explore differential transcription factor binding in distinct tissues and its role in disease. To probe differential Nkx2.1 binding in these tissues, we collected the MGE, hypothalamus, lung, and thyroid at embryonic day 13.5 (E13.5) and performed CUT&RUN to identify Nkx2.1 binding sites in each tissue. We also performed single cell Multiome assays to analyze gene expression and chromatin accessibility in Nkx2.1-expressing cells. By integrating gene expression, chromatin accessibility, and Nkx2.1 binding sites, we have gained mechanistic insight into differential Nkx2.1 function in distinct tissue. At some loci, differential accessibility in tissues drives differential Nkx2.1. binding. At other loci, accessibility is similar between tissue, implying that other regulatory mechanisms drive this differential binding. These insights improve our understanding of not only Nkx2.1 regulation during development, but also how transcription factors regulate distinct genetic programs in different tissue during development.

Disclosures: M.T. Manion: None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.05/F6

Topic: A.07. Development of Neural Systems

Support: Grants-in-Aid for Scientific Research JP26K02171
Grants-in-Aid for Scientific Research JP23K27324
Grants-in-Aid for Scientific Research JP20H03384

Title: Elucidation of liquid-liquid phase separation-dependent regulation in Dab1 signaling

Authors: *S. HIROSE, T. NOBUTA, K. UEMURA, T. KOHNO, M. HATTORI;
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Abstract: Dab1 is an intracellular adaptor protein essential for brain formation. Dab1-deficient mice exhibit severe abnormalities in the formation of the neocortex, hippocampus, and cerebellum. Dab1 functions downstream of the secreted glycoprotein Reelin. Upon binding of Reelin to its receptors, it is believed that Dab1 is phosphorylated by Src family kinases such as Fyn and transmits signals to multiple downstream proteins: however, how Dab1 exerts multiple and complicated functions is not well understood. We found that Dab1 contains intrinsically disordered regions (IDRs). Many proteins containing IDRs undergo liquid-liquid phase separation (LLPS), forming biomolecular droplets that contribute to intracellular signal transduction by concentrating or excluding specific molecules. We therefore hypothesized that the LLPS of Dab1 is important for mediating its downstream signaling functions. A fusion protein of Dab1 and glutathione-S-transferase (GST-Dab1) was expressed in E. coli, purified, and then cleaved at the GST domain. The addition of polyethylene glycol to Dab1 solution induced droplets in vitro. We next expressed GFP-fused Dab1 (Dab1-GFP) in COS-7 cells. At low expression levels, Dab1-GFP was diffusely distributed throughout the cytoplasm, whereas at high expression levels, it formed droplet-like structures. In low-expression cells, Dab1-GFP formed droplets upon the addition of sucrose to the culture medium. Furthermore, Dab1-GFP droplets in high-expression cells disappeared upon the addition of 1,6-hexanediol. Taken together, these results indicate that Dab1 undergoes LLPS both in vitro and in cells. To elucidate the physiological significance of Dab1 LLPS, we co-expressed GFP-fused Fyn (GFP-Fyn) with either mCherry-fused Dab1 (Dab1-mCherry) or its phosphorylation site mutant (Dab1-5F-mCherry). In cells co-expressing Dab1-mCherry and GFP-Fyn, Dab1 and Fyn were present within the same droplet, whereas this phenomenon did not occur with Dab1-5F-mCherry and GFP-Fyn. These results suggest that Dab1 undergoes LLPS under certain conditions and that Dab1 recruits Fyn into droplets in a phosphorylation-dependent manner, potentially facilitating Reelin-Fyn-Dab1 signaling. Our findings raise the possibility that LLPS serves as a molecular mechanism through which Dab1 achieves its diverse and complex signaling functions.

Disclosures: S. Hirose: None. **T. Nobuta:** None. **K. Uemura:** None. **T. Kohno:** None. **M. Hattori:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.06/F7

Topic: A.07. Development of Neural Systems

Support: UCLA Medical Scientist Training Program

Title: Investigating the roles of brain-enriched microproteins in neurodevelopment

Authors: *E. OSIGWE;
UCLA, Los Angeles, CA

Abstract: Geneticists have long regarded the human genome as mostly consisting of regulatory elements, with only an estimated 2% considered protein coding. However, recent technological advances, including in ribosome profiling and mass spectrometry, have revealed thousands of unannotated short open reading frames (sORFs). These sORFs may encode “microproteins” less than 100 amino acids in length and represent about 6% of unidentified protein-coding genes, including those missed in large-scale sequencing efforts in patients with neurodevelopmental disorders . However, characterization of the molecular functions of these microproteins first requires evidence of post-translational cellular interactions and confirmation of in vivo sORF translation in a vertebrate model. Here, we use zebrafish to show that F0 behavioral screening can be used as a proxy for disrupted neural circuitry and function, which can serve to prioritize candidates for functional characterization. Using F0 confirmed loss-of-function(LOF) “crispants,” we have identified candidate sORFs that showed deviations from their wild type siblings in baseline wake and sleep behaviors at the larval stage of development. Ongoing efforts to generate stable mutants, overexpression lines, and molecular characterization lines aim to uncover the functional roles of these microprotein candidates in neurodevelopment. We propose that our preliminary behavioral profiling to establish the effects of microprotein LOF can serve to streamline future sORF functional characterization studies. Ultimately, this work contributes to efforts to integrate behavioral, circuit, cellular, and molecular characterizations towards understanding the genetics of sORFs in neurodevelopment.

Disclosures: E. Osigwe: None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.07/F8

Topic: A.07. Development of Neural Systems

Title: Age-Dependent Cerebral Redox Vulnerability to Excitotoxic, Oxidative, and Mitochondrial Challenges

Authors: *J. LOPEZ HOLGUIN[1], N. PLAMENOV DONCHEV[1], V. PEREZ DE LA CRUZ[2]; [1]Physiol. Lab., Autonomous Univ. of Chihuahua, Chihuahua, Mexico; [2]Neurobiochemistry and Behavior Lab., Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico

Abstract: Postnatal development of the central nervous system (CNS) is influenced by the cerebral redox environment, which regulates synaptogenesis, dendritic maturation, and neuronal plasticity. Reactive oxygen species (ROS) contribute to physiological signaling during development; however, age-dependent changes in redox homeostasis may alter susceptibility to oxidative, mitochondrial, and excitotoxic insults. This study evaluated developmental differences in vulnerability to oxidative stress induced by ferrous sulfate ($FeSO_4$), mitochondrial dysfunction induced by 3-nitropropionic acid (3-NP), and excitotoxicity induced by quinolinic acid (QUIN). Prefrontal cortex homogenates were obtained from Wistar rats at postnatal days (PN) 3, 5, 9, 12,

and 30 (n = 5–6/group). Samples were incubated with $FeSO_4$, 3-NP, or QUIN. ROS production, lipid peroxidation, and mitochondrial function were assessed by biochemical tests and normalized to protein concentration. Basal ROS levels were significantly higher during early postnatal stages (PN3–PN9), consistent with elevated metabolic and synaptogenic activity. Exposure to $FeSO_4$, 3-NP, or QUIN did not further increase ROS production. In contrast, $FeSO_4$ significantly increased lipid peroxidation at all ages, with the greatest effects at PN12 and PN30. $FeSO_4$ and 3-NP significantly reduced MTT reduction from PN5 to PN30, indicating increased mitochondrial vulnerability during maturation. QUIN did not significantly affect ROS production, lipid peroxidation, or mitochondrial function. These findings indicate that early postnatal stages are characterized by elevated but tightly regulated redox activity, whereas later stages exhibit increased susceptibility to oxidative membrane damage and mitochondrial dysfunction. Developmental changes in redox homeostasis may contribute to age-dependent differences in neuronal vulnerability to oxidative and metabolic stress.

Disclosures: J. Lopez Holguin: None. **N. Plamenov Donchev:** None. **V. Perez De La Cruz:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.08/G1

Topic: A.07. Development of Neural Systems

Support: NIH grant ZIA NS002824-35

Title: Discovery of a Novel Readthrough Transcript: NSMF Meets ENTPD8

Authors: D. C. JACOBS[1], H. BOW[2], ***P. MANDAL**[1], J. SHORT[3], S. M. FARMER, Jr.[4], S. WRAY[1];
[1]NINDS, NIH, Bethesda, MD; [2]Interdepartmental Neurosci. Program, Univ. of Texas at Austin, San Luis Obispo, CA; [3]Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden; [4]GSBS, UTHealth Houston, Houston, TX

Abstract: The NMDA receptor synapto-nuclear signaling and neuronal migration factor (*Nsmf*) gene has been assigned distinct roles across species, mediating NMDA receptor synapto-nuclear signaling in the rat hippocampus while acting as a developmental guidance molecule involved in olfactory outgrowth and GnRH neuron migration in mice and humans, and being associated with Kallmann syndrome. Although NSMF in embryonic mouse has been reported to localize to cellular membranes, no transmembrane domain has been identified in its sequence using TMHMM 2.0. To reconcile these observations, we hypothesized the existence of a non-canonical **NSMF/Entpd8 readthrough transcript** that could append a membrane-compatible domain to NSMF. Readthrough transcripts, generated by transcription across two adjacent genes into a single mRNA, have been described in multiple species, including humans.To investigate this

possibility, we analyzed the transmembrane potential and sequence homology of NSMF-related proteins using SignalP, BLASTP, and pairwise sequence alignments. We then examined mouse tissue by RT-PCR, nested PCR, and Sanger sequencing. Canonical mouse NSMF isoforms lacked hydrophobic regions needed for membrane insertion. In contrast, previously uncharacterized NSMF-like proteins from three dolphin species and one bat exhibited approximately 50% N-terminal homology to mouse NSMF and contained an ENTPD8-like C-terminal region. These proteins showed strong conservation across the first 182-190 amino acids and included a predicted transmembrane domain.In mice, **Entpd8** is located 17.0 kb downstream of **NSMF** on chromosome 2 and is transcribed from the same strand. RT-PCR and nested PCR of cDNA prepared from E11.5 mouse tissue using Entpd8 exon 3/4-specific primers identified products of approximately 573 bp and 126 bp. Sanger sequencing confirmed that **NSMF exon 15** was joined to **Entpd8 exon 1** in both products. The larger amplicon contained a 422-bp linker region harboring multiple stop codons, making translation into a chimeric protein unlikely. In contrast, the smaller amplicon contained a 16-bp linker that maintained an open reading frame from NSMF into Entpd8, predicting a readthrough fusion protein.Together, these findings identify a novel **NSMF/Entpd8 readthrough transcript** that is predicted to encode a membrane-compatible, non-canonical NSMF isoform, providing a mechanistic framework for reinterpreting NSMF function in neuronal migration and its potential role in disease.

Disclosures: D.C. Jacobs: None. **H. Bow:** None. **P. Mandal:** None. **J. Short:** None. **S.M. Farmer:** None. **S. Wray:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.09/G2

Topic: A.02. Stem Cells and Reprogramming

Title: Retrotransposon transcripts control radial glia division mode in the developing neocortex

Authors: *Y. ZENG;
Tsinghua Univ., Beijing, China

Abstract: During mammalian corticogenesis, radial glial cells (RGCs) transition from symmetric proliferative to asymmetric neurogenic divisions, a key process that determines neuronal output and ultimately shapes brain size. However, whether transposable elements (TEs) regulate RGC division mode remains elusive. Here we identified a subset of TEs that are highly expressed in proliferative RGCs with a graded expression patterns across developing mouse cortex, hereby termed proliferative-RGC-expressing TEs (PRE-TEs). The bivalent histone marks on the PRE-TEs enables precise timing of their autonomous transcription, which is essential for maintaining RGC proliferation and supressing premature neurogenesis via cell-cycle regulation. PRE-TE transcripts act as chromatin-associated long non-coding RNAs that scaffold transcriptional condensates that directly promote the expression of cell cycle regulator, thus

sustaining the proliferative capacity of RGCs. Our findings reveal an underappreciated regulatory role of TE transcripts in governing RGC division mode during mammalian cortical development.

Disclosures: Y. Zeng: None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.10/G3

Topic: A.07. Development of Neural Systems

Support: ZIA NS002824-35

Title: Sweet Moves: Investigating the Role of O-GlcNAc Transferase in GnRH Neuron Migration

Authors: *Z. WILSON[1,2], P. MANDAL[3], S. WRAY[4], H. BOW[5], J. KEARNEY[6];
[1]Natl. Inst. of Neurolog. Disorder and Stroke, Damascus, MD; [2]NIH, Bethesda, MD; [3]NINDS, NIH, Bethesda, MD; [4]Cell. & Developmental Neurobio., NIH NINDS, Bethesda, MD; [5]Interdepartmental Neurosci. Program, Univ. of Texas at Austin, San Luis Obispo, CA; [6]Univ. of Virginia Sch. of Med., Charlottesville, VA

Abstract: Gonadotropin-releasing hormone (GnRH) neurons essential for reproductive function and fertility. During development, these neurons originate in the nasal placode and migrate into the forebrain, as such defects in migration can lead to reproductive disorders such as hypogonadotropic hypogonadism, Kallmann syndrome and infertility. O-GlcNAc transferase (OGT), the enzyme responsible for O-GlcNAc protein modification, regulates multiple developmental processes, yet its role in GnRH neuron migration remains unknown. We investigated the role of OGT in the developing olfactory-GnRH system of mice using genetic and pharmacological approaches. Embryonic nasal explants were used to assess GnRH neuron migration. Using immuno-cytochemistry, we found OGT protein in migrating GnRH neurons and olfactory sensory neurons. Pharmacological inhibition of OGT significantly increased GnRH neuronal migration, suggesting that OGT restrains GnRH neuronal movement. Conditional OGT knockout mice were generated using a Dulac-Cre; OGT floxed line, and GnRH neuronal distribution is being examined at embryonic day (E)12.5, E14.5, and adult, male and female mice by immunocytochemistry. Consistent with the in vitro findings, adult male OGT knockout mice exhibited a reduced number of GnRH neurons in the brain compared to control littermates. TurboID proteomic analysis was performed to identify OGT-associated proteins. Moesin, a cytoskeletal regulator of cell motility, was identified as one of the most highly enriched OGT-associated proteins and was further examined by immunofluorescence. Phosphorylated moesin localized predominantly to GnRH neuronal cell bodies at 4 and 7 days in vitro.These findings identify OGT as a novel regulator of GnRH neuron migration, highlight Moesin as a possible

mediator of this process and suggest that OGT-dependent cytoskeletal signaling contributes to establishment of the GnRH neuronal network required for normal reproductive function.

Disclosures: Z. Wilson: None. **P. Mandal:** None. **S. Wray:** None. **H. Bow:** None. **J. Kearney:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.11/G4

Topic: A.07. Development of Neural Systems

Title: Epiphytic Navigation of Serotonergic Axons Revealed by Organotypic Grafting and Holotomographic Live Imaging

Authors: *M. PICCHI[1], M. HINGORANI[2], S. MIGLIARINI[1], S. NAZZI[1], G. GIANNI[1], N. BARSOTTI[1], S. JANUSONIS[3], M. PASQUALETTI[1];
[1]Univ. of Pisa, Pisa, Italy; [2]Neurosci., Brown, Providence, RI; [3]Psychological and Brain Sci., Univ. of California Santa Barbara, Santa Barbara, CA

Abstract: Serotonin-producing neurons of the brainstem raphe nuclei generate one of the most extensive projection systems in the vertebrate central nervous system. In mice, serotonergic axons begin extending toward forebrain targets around embryonic day 11.5, reaching widespread destinations before birth and subsequently undergoing extensive arborisation to establish region-specific innervation patterns.Although considerable progress has been made in defining the molecular programs governing serotonergic neuron specification and differentiation, the mechanisms controlling axonal navigation during development remain poorly understood. Beyond canonical guidance cues, local tissue-derived signals are likely to play a critical role in shaping serotonergic axon trajectories. This view is supported by theoretical and experimental evidence suggesting that developing serotonergic axons display stochastic exploratory behaviour, allowing local environmental features to influence their growth. To investigate the contribution of the local tissue environment, we developed an ex vivo grafting assay in which serotonergic explants from Tph2-GFP mice were transplanted onto foetal brain flat-mounts or adult brain slices. Preliminary analyses indicate that both growth pattern and directionality are strongly influenced by graft location within the host tissue. In particular, serotonergic axons showed a pronounced tendency to align with and follow pre-existing fibre architectures, suggesting that local structural features provide important guidance information. To further characterise the cellular mechanisms underlying these interactions, we performed three-dimensional holotomographic imaging of embryonic serotonergic explants. Live imaging revealed highly dynamic growth cones and axon extension along other neurites. Collectively, these findings identify the local tissue environment as a key determinant of serotonergic axon behaviour, influencing both growth dynamics and directional choices in a context-dependent manner. This experimental platform provides a valuable framework for investigating how the physical and

geometric properties of the neural substrate interact with molecular guidance mechanisms to shape axonal trajectories. More broadly, our results support the view that serotonergic axons adopt an epiphytic-like growth strategy, relying on pre-existing structural elements of the tissue to guide their extension through complex neural environments.

Disclosures: M. Picchi: None. **M. Hingorani:** None. **S. Migliarini:** None. **S. Nazzi:** None. **G. Gianni:** None. **N. Barsotti:** None. **S. Janusonis:** None. **M. Pasqualetti:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.12/H1

Topic: A.07. Development of Neural Systems

Support: NIH/NIMH R01MH111674 (PI: Masaaki Torii)

Title: Plexin-A4 restrains caspase-dependent pruning of callosal axons during postnatal refinement

Authors: *A. K. SRIVASTAVA[1], D. J. DUTTA[2], R. KU[3], Y. M. MOROZOV[5], F. SUTO[6], P. RAKIC[7], K. HASHIMOTO-TORII[4], M. TORII[8];
[1]Ctr. for Neurosci. Res., Childrens Natl. Med. Ctr., Washington DC, DC; [2]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC; [3]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington D.C., DC; [4]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington DC, DC; [5]Dept Neurosci., Yale Univ. Sch. Med., New Haven, CT; [6]Natl. Inst. of Neuroscience, NCNP, Tokyo, Japan; [7]Dept. of Neurosci., Yale Univ. Sch. Med, Dept of Neurosci., New Haven, CT; [8]Ctr. for Neurosci. Res., Children's Natl. Hosp., Washington, DC

Abstract: The molecular programs that determine which corticocortical projections are retained or eliminated during postnatal corpus callosum refinement remain poorly defined. Here, we identify Plexin-A4, a semaphorin receptor best known for its role in embryonic axon guidance, as a postnatal regulator that limits excessive pruning of callosal axons. In mice, whole-axon elimination between postnatal day (P)4 and P10 coincided with caspase-dependent α-tubulin cleavage. During this period, Plexin-A4 protein transiently accumulated within axon shafts, whereas its mRNA remained restricted to neuronal somata, suggesting localized deployment within vulnerable projections. Using Cux2-CreERT2:Ai9/PlexinD1-GFP dual-reporter mice, we found that callosal projection neurons in layer II/III were preferentially affected by Plexin-A4 loss. Cholera toxin B retrograde tracing confirmed this laminar and regional vulnerability: Plexin-A4 knockout mice showed a greater loss of upper-layer corticocortical projections, including the long-range connectivity to the somatosensory cortex, compared to deeper-layer projections, despite normal midline crossing, lamination, and myelination. Consistent with a cell-autonomous role, in utero electroporation-mediated knockdown in layer II/III neurons reduced contralateral axon retention by P21 without altering initial midline crossing at P4, whereas

overexpression preserved axons normally eliminated. Mechanistically, Plexin-A4 deficiency enhanced caspase-dependent α-tubulin cleavage and autophagic flux without detectable actin cleavage, indicating selective microtubule vulnerability. Transient caspase inhibition partially rescued callosal axon loss. Finally, ex vivo activation of Plexin-A4 restricted to the midline axon shaft suppressed degeneration throughout the projection, whereas activation at somata or terminal arbors had no effect. Together, these findings identify Plexin-A4 as a spatially restricted regulator that restrains caspase-dependent pruning of corticocortical projections during postnatal refinement.

Disclosures: A.K. Srivastava: None. **D.J. Dutta:** None. **R. Ku:** None. **Y.M. Morozov:** None. **F. Suto:** None. **P. Rakic:** None. **K. Hashimoto-Torii:** None. **M. Torii:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.13/H2

Topic: A.07. Development of Neural Systems

Support: NIH R01 MH128745
NIH T32 NS141747
Andrew W. Mellon Predoctoral Fellowship, University of Pittsburgh

Title: Single-nuclei transcriptomic atlas of postnatal mouse paralaminar amygdala development reveals distinct immature neuron populations and maturation trajectories

Authors: *J. BAROUDI[1,2,3], N. SHVEDOV[2,3], S. F. SORRELLS[2,3];
[1]Ctr. for Neurosci. at the Univ. of Pittsburgh, Pittsburgh, PA; [2]Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [3]Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh & Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The paralaminar nucleus of the amygdala (PL) exhibits a prolonged developmental trajectory that extends into adolescence in humans and is characterized by a population of immature excitatory neurons that gradually mature throughout postnatal life. While the PL was recently identified in the mouse amygdala, the molecular heterogeneity of these neurons and the mechanisms regulating their delayed maturation remain poorly understood. Here, we present a single-nuclei RNA-sequencing atlas of mouse PL development across seven postnatal ages (P7, P14, P21, P28, P35, P47, and P60). Our hypothesis is that PL neurons comprise multiple molecularly distinct subtypes that differ in their developmental trajectories and responsiveness to maturation-associated signals. Following quality control and annotation of over 230,000 nuclei, we identified 4,079 high-confidence PL excitatory neurons and validated their identities using previously published PL transcriptomic dataset and reference cell types from the Allen Brain Atlas. Subclustering and pseudotime analyses revealed multiple PL neuronal populations spanning a continuum of maturation states, including transient immature populations present

predominantly during early postnatal life, maturing populations that emerge through adolescence, and a subset of persistently immature neurons that remain transcriptionally distinct into adulthood. Gene expression and ontology analyses demonstrated enrichment of developmental processes including neuronal migration, axonogenesis, and cell adhesion within immature populations, whereas mature populations were enriched for synaptic signaling, neurotransmission, and cellular metabolic pathways. Notably, trajectory analyses support the existence of two maturation programs within the PL: a delayed maturation pathway and an "ultra-delayed" pathway in which neurons retain immature molecular signatures through early adulthood. Finally, mature PL populations exhibited stronger activity-dependent transcriptional signatures than immature populations, and chemogenetic manipulations of the PL region suggest neuronal activity may contribute to maturation state transitions. Together, these findings establish a developmental transcriptomic framework for the PL and identify previously unrecognized neuronal subtypes and maturation trajectories that may underlie the unique developmental properties of this amygdala region.

Disclosures: J. Baroudi: None. **N. Shvedov:** None. **S.F. Sorrells:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR082.14/H3

Topic: A.07. Development of Neural Systems

Support: NIH Grant NS106244
NIH Grant EY022730

Title: Bursting in the Anterior Dorsal Nucleus of the thalamus predicts spontaneous movement in neonatal mice

Authors: *E. BOUCKOVA, T. BUSTAMANTE, M. T. COLONNESE;
Dept. of Pharmacol. and Physiol., The George Washington Sch. of Med. and Hlth. Sci., Washington, DC

Abstract: The developing nervous system uses discrete bursts of activity to drive synapse formation and elimination, maturation, and refinement. In sensory systems, these bursts are generated spontaneously in small regions of space and inform the development of sensory topography. In higher-order systems such as the association cortices and the limbic system, the generators and the early information conveyors are less well defined. In multiple systems, including motor and limbic (hippocampus and entorhinal cortex), sensory reafference generated by spontaneous jerks and startles is an important driver of early activity, a core output of which are early sharp waves (eSPW) in the hippocampus. But whether sensory references driving eSPWs are a universal organizer of limbic circuitry remains unknown. Here, we used head-fixed, unanesthetized neonatal C57BL/6J mice (7-9 days old) to examine the relationship between

movement, eSPWs, and spontaneous activity in the anterodorsal thalamic nucleus (ADn), a limbic relay that is a core component of ego-centric processing needed for spatial navigation and memory formation. Using synchronized high-density electrophysiology, electromyography, and videographic behavioral monitoring, we are analyzing the relationship between ADn and hippocampal activity, behavioral state, and spontaneous movements driving sensory reafferent input. In a preliminary group of 3 pups using piezo-electric based movement detection, ADn consistently preceded both hippocampal eSPWs by ~100ms and spontaneous jerks and twitches by ~50ms. Together, our results suggest an important early divergence in the activity driving egocentric vs allocentric processing. The ADn appears to produce spontaneous bursts in response to the motor corollary discharge, and thus encodes the internal state of the animal, rather than the external world resulting from the motor reference reaching hippocampal circuits.

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

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.15/H4

Topic: A.07. Development of Neural Systems

Support: NIH R21MH129995-01

Title: Developmental origins of functional diversity of medial amygdala output neurons for male aggression

Authors: *A. ABBONDANZA[1], A. ABU IRQEBA[2], L. HEIER[2], M. TEMAM[2], A. RIVERA[2], L. WANG[2], J. G. CORBIN[2];
[1]Children's Natl. Med. Ctr. / Ctr. for Neurosci. Res., Washington, DC; [2]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC

Abstract: The medial amygdala (MeA) is a major nucleus for processing social behavior. It is essential for the expression of innate social behaviors in rodents, making it an ideal system to study how developmental programs guide the formation of circuits that drive these behaviors. The MeA comprises multiple excitatory and inhibitory subtypes of output neurons, which are in large part defined by the expression of different transcription factors during embryonic and/or post-natal stages. Our previous and collaborative studies have demonstrated that inhibitory MeA output neurons marked by the transcription factor encoding gene, *Foxp2,* are selectively engaged during male aggressive social interactions and are both necessary and sufficient to drive male aggression via connections to the BNST and hypothalamus (Lischinsky et al., 2017; 2023). However, when and how these aggression neurons arise during development, and how their identity is linked to circuit assembly, is not understood. Using developmental single-nuclei RNA sequencing of the MeA, we identified three distinct Foxp2^{+} output neuron subtypes marked by different combinations of transcription factor and cell adhesion molecule encoding genes. Our

analyses indicate that these subtypes diverge developmentally well before aggressive behaviors emerge, have specific patterns of connectivity, and are activated during different components of male aggressive behavior. Together our work links neuronal subtype specification, circuit assembly, and adult sexually dimorphic social behaviors in the MeA.

Disclosures: A. Abbondanza: None. **A. Abu Irqeba:** None. **L. Heier:** None. **M. Temam:** None. **A. Rivera:** None. **L. Wang:** None. **J.G. Corbin:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.16/H5

Topic: A.02. Stem Cells and Reprogramming

Support: Brain Research Foundation

Title: Heterochromatin-Mediated Propagation of Transcriptional States in Neural Stem Cells

Authors: *S. WARREN;
Indiana Univ. Bloomington, Bloomington, IN

Abstract: Epigenetic memory refers to the ability of cells to maintain stable transcriptional states after the environmental signals that initially established them have been removed[1]. Histone H3 lysine 9 trimethylation (H3K9me3), a hallmark of heterochromatin, has been implicated in the maintenance of cellular identity[2]. However, the role of H3K9me3 in preserving transcriptional states in proliferating neural stem cells (NSCs), remains poorly understood. Here, we use a mouse model expressing a doxycycline (dox)-inducible mutant histone H3 transgene carrying a lysine 9-to-methionine substitution (H3K9M), which enables transient and widespread depletion of H3K9me3[3]. Upon dox administration, H3K9M inhibits the activity of the H3K9 methyltransferases SUV39H1, SUV39H2, and SETDB1, resulting in global loss of H3K9me3. Withdrawal of dox restores H3K9me3 levels, allowing the examination of both the loss and recovery of H3K9me3-marked heterochromatin. Using this system, we investigated the role of H3K9me3 in sustaining epigenetic memory in NSCs isolated from the embryonic cerebral cortex. Using a combination of cellular, molecular, and genomic approaches, we characterized the effects of transient H3K9me3 depletion on chromatin accessibility and gene regulation and assessed whether these changes persist following restoration of H3K9me3. Together, our findings provide insight into the mechanisms by which H3K9me3-mediated heterochromatin contributes to epigenetic memory and the maintenance of stable cell states within the neural lineage.

Disclosures: S. Warren: None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.17/H6

Topic: A.07. Development of Neural Systems

Support: German Research Foundation (DFG) - Project number 512746157
German Research Foundation (DFG) - Project number 514060831

Title: Transcriptional Logic Governing Brainstem Neuronal Diversity

Authors: F. MENG[1,2], Y. MOU[1,2], ***L. R. HERNANDEZ-MIRANDA**[3,2,1];
[1]Charite – Universitatsmedizin Berlin, Berlin, Germany; [2]Inst. for Mol. and Cell. Anat., [3]Univ. Ulm, Ulm, Germany

Abstract: The brainstem contains highly complex neuronal circuits that regulate essential physiological processes, including respiration, motor coordination, and the integration of diverse sensory stimuli that together support bodily homeostasis. Despite its fundamental importance, the molecular and developmental diversity of brainstem neurons, as well as the mechanisms through which distinct neuronal populations become incorporated into functional circuits, remains underexplored. Here, we combined complementary single-cell omics approaches with chromatin immunoprecipitation followed by deep sequencing, and computational analysis to investigate the transcriptional mechanisms governing brainstem neuronal diversification. Our analyses provide a molecular and functional characterization of the transcription factor logic controlling the specification, differentiation, and maturation of four molecularly distinct brainstem neuronal populations. By integrating developmental gene-expression profiles, chromatin-state information, and transcription factor binding data, we identified regulatory programs that distinguish these neuronal populations and define their developmental trajectories. We further examined how these molecularly defined neuronal types contribute to brainstem circuits involved in somatosensory processing, respiratory control, and motor function. Together, our findings establish a mechanistic framework linking transcriptional regulation during embryonic development to the generation of specialized neuronal identities and their subsequent incorporation into functionally distinct brainstem networks. These results advance our understanding of brainstem organization and provide a foundation for investigating how disruption of developmental gene-regulatory programs may contribute to neurological disorders affecting sensory, respiratory, and motor functions.

Disclosures: F. Meng: None. **Y. mou:** None. **L.R. Hernandez-Miranda:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.18/H7

Topic: A.02. Stem Cells and Reprogramming

Support: Swiss National Science Foundation

Title: Distinct NOTCH1 and NOTCH2 signaling pathways regulates neural stem cell activation and maintenance in mouse adult neurogenesis

Authors: *E. MAES[1], V. TAYLOR[2], A. LAMPADA[2];
[1]Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland; [2]Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland

Abstract: Tight regulation of neural stem cell (NSC) maintenance and differentiation is essential for central nervous system development and adult neurogenesis. In the adult brain, neurogenesis remain active in two specialized niches: the ventricular-subventricular zone (V-SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). Notch signaling is a key regulator in both niches, with multiple receptors—including NOTCH1, NOTCH2, and NOTCH3—expressed in adult NSCs. Previous work from our group showed that NOTCH1 and NOTCH2 are co-expressed in NSC populations, where they exert distinct and opposing functions on adult neurogenesis. NOTCH1 primarily acts on activated NSCs, and its deletion leads to their differentiation and depletion, whereas loss of NOTCH2 activates dormant NSCs, expands the active NSC pool, and increases neurogenesis. Importantly, deletion of RBPJk, the canonical downstream effector of Notch signaling, phenocopies the combined loss of NOTCH1 and NOTCH2, raising the question of how receptor-specific outcomes are achieved through a shared signaling effector. To address this, we generated CRISPR/Cas9-engineered transgenic mouse lines expressing endogenous 3xFLAG-tagged NOTCH1 or NOTCH2 proteins. Using chromatin immunoprecipitation followed by sequencing (ChIP-seq) and immunoprecipitation-mass spectrometry (IP-MS), we mapped the transcriptional targets and protein interactors of NOTCH1, NOTCH2, and RBPJk in adult V-SVZ NSCs. Our findings reveal distinct molecular mechanisms underlying NOTCH1 and NOTCH2-mediated regulation of NSC states, providing new insight into receptor-specific Notch signaling and its role in balancing stem cell quiescence and activation during neurogenesis.

Disclosures: E. Maes: None. **V. Taylor:** None. **A. Lampada:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.19/H8

Topic: A.02. Stem Cells and Reprogramming

Support: NIH IRP funding HD008962
FY25 NICHD Career Development Awards
FY26 Early Career Fellowship Award

Title: A Perturb-seq CRISPR screen to identify transcription factors promoting CGE-derived interneurons

Authors: *A. CHAUHAN[1], D. R. LEE[2], T. J. PETROS[3];
[1]NICHD, NIH, Bethesda, MD; [2]Unit on Cell. and Mol. Neurodevelopment, NIH/NICHD, Bethesda, MD; [3]Developmental Neurosci. Br., NICHD/Eunice Kennedy Shriver Nat'l Inst. of Child H, Rockville, MD

Abstract: Forebrain GABAergic interneurons originate from the medial and caudal ganglionic eminence (MGE & CGE). While some genes driving MGE-derived interneuron development have been well-characterized, mechanisms regulating CGE-derived interneurons remains largely unexplored. Interestingly, humans have an increased percentage of CGE-derived interneurons relative to mice, and some diseases such as tuberous sclerosis complex (TSC) are directly linked to dysfunction of CGE cells. Thus, defining genes that drive CGE cell fate is critical to understand both normal development and disease etiologies. Here we perform a CRISPR Perturb-seq experiment to identify candidate transcription factors (TFs) that promote CGE fate. We generated 2 mESC lines with Cas9 linked to an activator or repressor. We retrofitted these mESCs with a fluorescent CGE reporter (*Nr2f2-RFP*) to detect CGE-fated cells. Further, we generated a Lentiviral library of gRNAs (*GFP*-tagged) targeting ~900 TFs expressed in the embryonic mouse brain. By collecting Lentiviral-infected GFP+ and RFP+ (yellow) cells, we will identify candidate genes whose activation or repression promotes CGE fate.

Disclosures: A. Chauhan: None. **D.R. Lee:** None. **T.J. Petros:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.20/I1

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

Support: 1U19MH114830-01

Title: A High-Resolution Spatial Transcriptomic Atlas of Embryonic Mouse Brain Development Using Takara Trekker and 10x FLEX

Authors: *J. XIE[1], A. RUIZ[1], T. CARDENAS[1], J. GOLDY[1], A. OYAMA[1], J. WILHELMY[2], J. SAKKOS[2], T. HUI[2], S. Y. CHENG[1], Y. GAO[1], A. CHAKKA[1], A. TORKELSON[1], A. REECE[1], J. ARIZA TORRES[1], K. SMITH[1], Z. YAO[1], H. ZENG[1], C. VAN VELTHOVEN[1];
[1]Allen Inst., Seattle, WA; [2]Takara Bio, San Jose, CA

Abstract: The developing brain is a highly dynamic system in which stem cells, progenitors, and newborn neurons interact with their local tissue microenvironment to orchestrate neurogenesis and gliogenesis. Despite its fundamental importance, a comprehensive spatially resolved single-cell atlas spanning multiple embryonic stages has remained lacking. Imaging-based spatial transcriptomics approaches face substantial technical challenges in densely packed germinal regions such as the ventricular zone, where cells are small, rapidly dividing, and tightly compacted, making accurate cell segmentation a persistent bottleneck that compromises downstream analysis. To overcome this, we employed Takara Trekker, a sequencing-based spatial transcriptomics platform that bypasses the requirement for cell segmentation entirely. Using a larger tile format with an increased surface area than previous Trekker iterations, we achieved broader coverage of complex brain architecture within a single experiment. Combined with the multiplexed 10X FLEX assay, this approach maximized scalability across samples and timepoints. Serial tissue sections were collected at defined intervals, together capturing regional transcriptomic gradients across both the anterior-posterior and mediolateral axes of the embryonic brain. Through integration of the single-nucleus spatial transcriptomic dataset and a single-cell RNA-seq atlas, we derive a high-resolution cell type taxonomy of the embryonic mouse brain, resolving neuronal and non-neuronal populations across key developmental timepoints. Anchoring this taxonomy in space, we map the spatial organization of cell types across embryonic brain regions, providing a framework to investigate the spatial logic of cell type diversification, lineage progression, and regional specification during neurogenesis. Collectively, this work established a foundational resource for the neurodevelopmental community to explore the molecular and spatial underpinnings of embryonic brain development.

Disclosures: J. Xie: None. **A. Ruiz:** None. **T. Cardenas:** None. **J. Goldy:** None. **A. Oyama:** None. **J. Wilhelmy:** None. **J. Sakkos:** None. **T. Hui:** None. **S.Y. Cheng:** None. **Y. Gao:** None. **A. Chakka:** None. **A. Torkelson:** None. **A. Reece:** None. **J. Ariza Torres:** None. **K. Smith:** None. **Z. Yao:** None. **H. Zeng:** Other; H.Z. is on the scientific advisory board of MapLight Therapeutics, Inc.. **C. van Velthoven:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.21/I2

Topic: A.04. Transplantation and Regeneration

Support: National Eye Institute Grant 1R01EY033000
National Eye Institute Grant 1R01EY034325
National Eye Institute Grant 1K08EY032991
Core Center for Vision Research Grant P30 EY001765
Foundation Fighting Blindness Grant RC-CMM-0824-0899-JHU
Fight for Sight-International Retinal Research Foundation FFSGIA16002

Title: Imaging Guided Subretinal Transplantation of Human Induced Pluripotent Stem Cells Differentiated to RPE for Treatment of Age-related Macular Degeneration

Authors: *P. NGUYEN[1], W. QIAN[2], A. FAHIM[3], Y. PAULUS[4];
[1]Johns Hopkins Universtiy, Sch. of Med., Baltimore, MD; [2]Imra America Inc.,, Ann Arbor, MI; [3]Ophthalmology and Visual Sciencesph, Michigan Univ., Ann Arbor, MD; [4]Ophthalmology, John Hopkins Univ., Baltimore, MD

Abstract: Degeneration of retinal pigment epithelium (RPE) cells contributes significantly to vision loss in disorders including age-related macular degeneration (AMD) and retinitis pigmentosa (RP). Replacement of damaged RPE using human induced pluripotent stem cells differentiated to RPE (hiPSC-RPE) cells has emerged as a promising regenerative strategy. However, successful clinical translation requires reliable methods for monitoring transplanted cells over extended periods in vivo. Here, we developed a multimodal imaging approach for long-term visualization of transplanted hiPSC-RPE cells in a rabbit model of retinal injury. Localized RPE degeneration was induced in albino rabbits using a 532 nm laser photocoagulation protocol (800 mW, 500 μm spot size, 100 ms duration, 12 lesions per eye). hiPSC-RPE cells were labeled with chain-like gold nanoparticle clusters functionalized with nuclear localization sequence (NLS) peptides and indocyanine green (ICG) dye to enhance multimodal optical contrast. 1×10^5 labeled cells were transplanted into the subretinal space using optical coherence tomography (OCT) guidance following retinal photocoagulation. Animals were longitudinally monitored using a custom imaging platform integrating photoacoustic microscopy (PAM), OCT, and fluorescence imaging. Photoacoustic imaging provided strong contrast enhancement that enabled clear localization of transplanted cells from endogenous retinal and choroidal vasculature, particularly at 650 nm excitation. OCT imaging demonstrated gradual restoration of damaged retinal architecture and improved integrity of the RPE region over time. Fluorescence imaging confirmed localization of transplanted cells during the early post-transplantation period. Longitudinal monitoring demonstrated survival and retention of transplanted cells for up to six months in vivo. Histological assessment and immunofluorescence staining further verified engraftment of hiPSC-RPE cells within injured retinal regions and suggested partial reconstruction of the disrupted RPE layer. These findings demonstrate the utility of PAM/OCT/fluorescence imaging for long-term evaluation of hiPSC-RPE in retinal disease models. The combination of nanoparticle-based cellular labeling and multimodal imaging provides a valuable platform for studying stem cell survival, migration, and tissue integration following transplantation. This work further supports the therapeutic potential of hiPSC-RPE transplantation for retinal neurodegenerative disorders and may contribute to the development of clinically translatable regenerative therapies for vision preservation.

Disclosures: P. Nguyen: None. **W. Qian:** None. **A. Fahim:** None. **Y. Paulus:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.22/I3

Topic: A.04. Transplantation and Regeneration

Support: NIH Grant EY034325

Title: Ratiometric Photoacoustic Imaging Enables Longitudinal In Vivo Assessment of Stem Cell Viability

Authors: *S. PARK[1], P. NGUYEN[5], W. QIAN[6], J. FOLZ[2], N. PERERA[3], A. FAHIM[4], Y. PAULUS[7], X. WANG[2];
[1]Biomed. Engin., Univ. of Michigan, ANN ARBOR, MI; [2]Biomed. Engin., [4]Dept. of Ophthalmology and Visual Sci., [3]Univ. of Michigan, Ann Arbor, MI; [5]Ophthalmology, Johns Hopkins Universtiy, Sch. of Med., Baltimore, MD; [6]IMRA America, Inc., Ann Arbor, MI; [7]Johns Hopkins Univ., Baltimore, MD

Abstract: Stem cell transplantation is a promising strategy for numerous neurodegenerative diseases such as geographic atrophy from macular degeneration. However, longitudinal monitoring of transplanted stem cells remains challenging because of the limited functional imaging information beyond structural localization. Here, we developed a multimodal imaging system integrating photoacoustic microscopy (PAM) and optical coherence tomography (OCT) with a reactive oxygen species (ROS)-responsive nanoprobe for noninvasive assessment of transplanted cell viability. Human induced pluripotent stem cell-derived retinal pigment epithelium (hiPSC-RPE) cells were labeled with chain-like gold nanoparticle clusters conjugated to the ROS-sensitive near-infrared dye IR775c (CGNP-IR775c). Under oxidative stress, CGNP maintains stable optical absorption, whereas IR775c undergoes signal loss, enabling ratiometric viability assessment. CGNP-IR775c-labeled hiPSC-RPE cells were subretinally transplanted into healthy New Zealand White rabbits (2-6 months, 2.6 - 3.2 kg, both sexes). Apoptosis was induced 4 days after transplantation using a 532 nm photocoagulation laser (100 mW, 300 μm spot size, 1s exposure). Longitudinal imaging was performed up to 14 days using fundus photography, triple-wavelength PAM (532 nm, 620 nm, 775 nm), and OCT. PAM visualized retinal vasculature, transplanted cell distribution and viability, while OCT provided anatomical localization. Non-laser-irradiated areas maintained stable ratiometric values (I_{775}/I_{620}) near 1.0 over 14 days, indicating consistent viability and successful engraftment. In contrast, laser-irradiated areas showed an immediate decrease and progressive decline to 0.2-0.3 by day 14, consistent with oxidative stress and apoptosis. Histological analysis revealed preserved retinal architecture in non-irradiated regions and localized structural disruption after laser exposure. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay showed significantly increased apoptosis in laser-irradiated regions compared with controls (87.5±3.6% vs. 4.7±3.1%, **$p \leq 0.01$, n=5) and spatially corresponded with reduced PAM ratios. Minimal TUNEL positivity and normal retinal architecture in non-laser-irradiated regions suggest that CGNP-IR775c labeling and multimodal imaging did not induce detectable local toxicity. These findings demonstrate that ROS-responsive ratiometric photoacoustic imaging enables quantitative, longitudinal assessment of transplanted stem cell viability and establishes a functional imaging framework for evaluating regenerative therapies *in vivo*.

Disclosures: S. Park: None. **P. Nguyen:** None. **W. Qian:** None. **J. Folz:** None. **N. Perera:** None. **A. Fahim:** None. **Y. Paulus:** None. **X. Wang:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.23/I4

Topic: A.07. Development of Neural Systems

Support: WISE Program of Kanazawa University by MEXT; JST SPRING, JPMJSP2135
JST CREST JPMJCR24B2
KAKENHI JP 25K22468

Title: Spatial mapping of mechanical properties in the mouse hippocampus using ex vivo SIM-AFM

Authors: *I. SHIOKA[1], J. NAGAI[3], H. KAWASAKI[4], S. OKUDA[2];
[1]Grad. Sch. of Frontier Sci. Initiative, Kanazawa Univ., Kanazawa, Japan; [2]Kanazawa Univ., Kanazawa / Ishikawa, Japan; [3]RIKEN Ctr. for Brain Sci., Saitama, Japan; [4]Sch. of Med, Kanazawa Univ., Ishikawa, Japan

Abstract: The mechanical properties of brain tissue may play important roles in regulating developmental cellular processes, including neurogenesis, neuronal migration, and dendritic growth. Indeed, in vitro studies have demonstrated that these cellular behaviors are regulated by the mechanical properties of the cellular microenvironment. For example, soft substrates promote neuronal differentiation, whereas stiff substrates favor glial differentiation. However, the biological roles of tissue mechanics remain poorly understood, partly because comprehensive methods for elucidating the spatial distribution of mechanical properties, their spatiotemporal changes, and their relationship to cellular dynamics in vivo are lacking. In this study, we aimed to establish a methodological framework for investigating the biological roles of tissue mechanics by quantitatively elucidating the spatial distribution of stiffness and correlating it with molecular distributions in mouse hippocampus during development. First, we developed an ex vivo SIM-AFM platform that combines structured illumination microscopy (SIM) and atomic force microscopy (AFM) to correlate the distribution of stiffness with molecular distributions under ex vivo conditions. Using this approach, we measured hippocampal regions of mouse brain coronal sections from mice at different developmental stages. In addition, we developed a novel alignment analysis method to correct for morphological variability among individual mice and enable comparison of spatial stiffness patterns across experimental conditions. As a result, we revealed heterogeneous stiffness distributions corresponding to the complex anatomical organization of the hippocampus, as well as its dynamic changes during development. Furthermore, statistical analyses using conventional analyses, Functional Data Analysis (FDA), and Cluster-based Permutation Testing (CP test) demonstrated significant developmental changes in stiffness patterns at three hierarchical levels: regional mean values, global spatial distributions, and localized subregions. Our methods can be extended to tissues from aging and disease model mice and provide a foundation for comprehensively understanding the mechanical microenvironment of tissues and its biological significance.

Disclosures: I. Shioka: None. **J. Nagai:** None. **H. Kawasaki:** None. **S. Okuda:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.24/I5

Topic: A.07. Development of Neural Systems

Support: National Institute of Neurological Disorders and Stroke, R01NS138781

Title: Molecular mechanisms regulating the neural extracellular matrix during vocal development in songbirds.

Authors: *C. N. ASOGWA, B. M. COLQUITT;
Dept. of Molecular, Cell, and Developmenntal Biol., Univ. of California, Santa Cruz, Santa Cruz, CA

Abstract: The extracellular matrix (ECM) has emerged as a major regulator of neurogenesis/ or neural plasticity in both vertebrates and invertebrates. However, the exact molecular factors that underlie ECM regulation and their contributions to neural plasticity remain poorly understood. The vocal-control brain circuits (song system) of songbirds are an excellent model to investigate the molecular factors that regulate the ECM and their contributions to the age-related changes in neurogenesis that characterize the song system during the critical period of learned vocal development. To address this knowledge gap, we first examined single-nucleus RNA sequencing (snRNA-seq) data from our lab and found that a group of genes (A Disintegrin And Metalloproteinase with ThromboSpondin motifs, ADAMTSs), which encode secreted ECM-digesting enzymes, are differentially regulated in HVC, a brain nucleus important for song production in songbirds. verify this, we evaluated using fluorescence *in situ* hybridization, the expression of ADAMTS5, ADAMTS6, and ADAMTS19in HVC (a vocal-control brain nucleus) of male Bengalese finches during the critical period of vocal learning, using fluorescence in situ hybridization, a vocal-control brain circuit, of male Bengalese finches during the critical period. The results support a differential regulation of ADAMTS5, ADAMTS6, and ADAMTS19 in HVC across the three stages of vocal development: subsong, plastic song, and crystallized song, suggesting that these ADAMTS genes may influence the neuroplasticity of vocal learning. To understand the contributions of these genes to vocal learning, we first cloned and overexpressed ADAMTS19 in 3T3 cells, and then designed three short-hairpin RNA (shRNA) constructs to knock down ADAMTS19 *in vitro*. Currently, we have validated ADAMTS19 overexpression using qPCR and are testing the knockdown efficiencies of the shRNA constructs. Next, we will inject the most efficient shRNA into HVC of male finches at the different stages of song learning to evaluate the effects of ADAMTS19 knockdown on ECM status and neurogenesis. These initial findings highlight potential molecular mechanisms regulating the ECM in a brain circuit important for learned vocal development.

Disclosures: C.N. Asogwa: None. **B.M. Colquitt:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.25/I6

Topic: A.07. Development of Neural Systems

Support: NINDS (R56 NS110951)
NINDS (RO1 NS128286)

Title: Developmental and experience-dependent regulation of thyroid hormone signaling during sensory learning

Authors: *A. BATISTUZZO, S. E. LONDON;
Psychology, Univ. of Chicago, Chicago, IL

Abstract: Thyroid hormone (TH) signaling regulates neural development across vertebrates, influencing neuronal maturation, synaptogenesis, myelination, and plasticity. However, little is known about how TH-related pathways are regulated in the context of developmental learning. To examine TH signaling in the zebra finch auditory forebrain lobule (AL), required for both males and females to learn and a locus for a canonical critical period in males, we combined several molecular methods. RT-qPCR performed on AL and diencephalon (dien) across posthatch development (Posthatch day (P)1-adult) revealed developmental RNA levels. MCT8 mRNA peaked P1-P10 and then declined, while DIO2 was low at P1, increasing at P23 and decreasing progressively until adulthood. THRA exceeded THRB and increased between P1 and P23/P30, remaining relatively stable thereafter, whereas THRB peaked at P23, declined during the male critical period (P30-60), and increased again by P67 and adulthood. Expression levels appeared consistently higher in AL than dien for DIO2, DIO3, THRA, and THRB across all ages, while DIO1 and MCT8 were more comparable. Trajectories were similar for DIO1, DIO2, and MCT8, but diverged for DIO3 and THRB: DIO3 declined sharply after P1 in dien but remained relatively stable in AL, whereas THRB showed a pronounced P23 peak and sharp P30 decline in AL that was not observed in dien. Immunoprecipitation-based riboTRAP of baseline (silence) ribosome-associated transcripts revealed age-dependent differences in males, including THRA, THRB, MCT8, NCOA2, NCOR1, and KLF9 from the P67-to-adult transition. Song exposure further modulated TH pathway-associated transcripts. At P23, females showed increased RELN ribosome association and reduced myelination-associated genes (MBP, PLP1, and CNP), and P60 males showed increased ribosome association of TH receptors and receptor-associated signaling components (THRA, THRB, NCOA2, and NCOR1); these responses were reduced in adulthood. Preliminary single nucleus analyses identified THRB enrichment across excitatory neuron clusters (EX-2, EX-3, EX-5, and EX-6) and D1R-expressing neurons in P23/P30 male and female AL. Together, these findings demonstrate that TH signaling in the AL is dynamically regulated across development at multiple levels, including transport, local activation, receptor expression, receptor-associated signaling, and sensory experience. The coordinated developmental and song-dependent regulation of THRB and associated signaling

components suggests that local control of TH responsiveness may contribute to maturation of neural circuits that support developmental learning.

Disclosures: A. Batistuzzo: None. **S.E. London:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.26/I7

Topic: A.02. Stem Cells and Reprogramming

Support: Neurological Disorders and Stroke R01NS138781

Title: Shared Origins, Specialized Ends: Tracing the Developmental Lineage of Songbird Vocal Circuits

Authors: *F. F. RAND, IV[1], B. COLQUITT[1], A. P. MARQUEZ[2], C. LAGOUSIS[3];
[1]Univ. of California Santa Cruz, Santa Cruz, CA; [2]Molecular, Cellular, and Developmental Biol., UC Santa Cruz, San Jose, CA; [3]Univ. of California, Santa Cruz, Santa Cruz, CA

Abstract: Songbirds learn their vocalizations using dedicated forebrain circuits built from specialized neuron types that arerare across the animal kingdom, making them a uniquely powerful model for how these neurons develop. Howthese circuits arise, however, remains unknown. These neurons occupy discrete pallial nuclei such as HVC, posi-tioned immediately adjacent to non-song pallium, an ideal setting to ask whether specialized and general neurontypes share a developmental lineage. Two models compete, hypothesizing that song and non-song neurons mayarise from dedicated progenitor pools, or from shared radial glial progenitors whose output is biased by spatialcontext. Mature transcriptomic identity cannot distinguish these possibilities, because identical adult cell typescan arise from either fixed or context dependent specification, so a direct lineage readout is required. To addressthis, we developed a barcoded clonal lineage tracing pipeline in the Bengalese finch (*Lonchura striata domestica*)using an iOn piggyBac cassette carrying a STICR barcode library, delivered by post-hatch in vivo electroporationto permanently label radial glial progenitors and their progeny. Labeled cells were recovered by single-nucleusRNA sequencing (snRNA-seq) of microdissected HVC and adjacent non-song pallium. Cell type identities wereassigned by label transfer from published finch atlases, returning song glutamatergic, non-song glutamatergic,GABAergic, neurogenic, and glial calls, and clones were reconstructed by matching three variable STICR bar-code segments. In an exploratory pilot using four male finches at roughly 100 days post-hatch, we profiled 24,537nuclei resolving 48 cell types, recovered 13 STICR barcoded cells, and reconstructed fate calls for each recoveredclone. These results show that the full workflow, from barcoded post-hatch electroporation through snRNA-seqto clonal reconstruction, runs end to end on finch tissue and yields interpretable per clone fate data. Barcoderecovery in this pilot was low and underpowered for definitive lineage conclusions, so we report it as a feasibilityresult rather than

a test of the competing models. To our knowledge this is the first barcoded clonal lineage tracingplatform in songbird, and the first applied to specialized complex motor neurons such as those that make up thesong system. It establishes that song and non-song lineages can be recovered and lays the foundation for apowered test of shared versus dedicated progenitor origins.1

Disclosures: F.F. Rand: None. **B. Colquitt:** None. **A.P. Marquez:** None. **C. Lagousis:** None.

Poster

PSTR082: Mechanisms of Neurodevelopment in Animal Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR082.27/I8

Topic: A.07. Development of Neural Systems

Support: NINDS (R56 NS110951)
NINDS (R01 NS128286)

Title: Insights into ERK-Dependent Sensory Song Learning in Zebra Finches

Authors: *K. V MAHESHWAR[1], H. TAI[2], S. CHARI[2], S. E. LONDON[1];
[1]Psychology, [2]Univ. of Chicago, Chicago, IL

Abstract: Juvenile male and female zebra finches undergo developmental song learning leading to life-long behavioral consequences. Adult males sing songs that are close copies of the song they were exposed to during development. Developmental song exposure in females shapes their song preference in adulthood. Overlaps in developmental learning periods and auditory processing circuitry in males and females raise the question of the extent to which sensory song learning is supported by shared molecular mechanisms. While in males, disruption of ERK (extracellular signal-regulated kinase) signaling during developmental song experience impairs adult song copying, whether this pathway is similarly required for song learning in females remained unknown. Here, we pharmacologically inhibited ERK activation in the auditory forebrain lobule (AL) of juvenile females during controlled song exposure and the effect of this manipulation on adult song preference was assayed using an operant conditioning perch-hop assay. Females infused with ERK inhibitor showed no tutor song bias, while untreated and control infusion birds did. The juvenile's engagement with the tutor during these sessions was analyzed as a measure of social interest was noted to be unaffected by ERK inhibition. We thus show, that ERK signaling in juvenile female AL during tutor experience is required for adult song preference through mechanisms independent of social engagement. Given that ERK signaling is necessary for developmental song learning in both sexes, we next confirmed that song evokes phosphorylation of ERK at ages significant for developmental sensory song learning. Preliminary results are consistent with our prediction that song induces ERK phosphorylation in males and females during a developmentally relevant age for sensory song learning. Additionally, using catFISH in adult females, we examined if ERK disruption during

development alters AL responses to tutor and novel song. We hypothesize that developmental disruption of ERK will reduce differential responses of cells in the AL to tutor song in adulthood. Collectively, this work broadens our understanding of the molecular machinery underlying developmental learning, highlighting ERK-dependent plasticity as a shared feature of sensory song learning regardless of behavioral output.

Disclosures: K. V Maheshwar: None. **H. Tai:** None. **S. Chari:** None. **S.E. London:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR083.01/J1

Topic: B.04. Synaptic Transmission

Support: NIH R00 MH118425
NARSAD BBRF Young Investigator Award
T32MH119049-07
T32NS04554016
UCI - Eugene Cota-Robles Fellowship

Title: Investigating the role of neuropsychiatric disorder-associated cell adhesion molecule MDGA1 in synaptic function and behavior

Authors: *M. A. SANDOVAL, M. LU, L. BUI, J. DÍAZ-ALONSO;
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Abstract: Encoding mutations of the cell adhesion molecule, MDGA1, have been associated with neuropsychiatric disorders in multiple populations. However, the brain region-specific role of MDGA1 disruption in cognitive dysfunction remains unclear. Here, we have identified MDGA1 labeling restricted to the inner molecular layer (iML) of the dentate gyrus (DG), implying expression in DG hilar mossy cells (hMCs). Intriguingly, hMC dysregulation has been recently implicated in multiple forms of cognitive impairment found across psychiatric disorders, making putative hMC-derived MDGA1 a promising therapeutic research target. We initially crossed floxed MDGA1 (MDGA1$^{f/f}$) mice with a commonly used Dopamine 2 receptor-encoding Cre driver line (*Drd2*-Cre) driver line (Drd2-cre::MDGA1$^{f/f}$ mice) to target hMCs. We observed a significant loss of MDGA1 signal within the iML in Drd2-cre::MDGA1$^{f/f}$ mice compared to controls (n = 3 mice / genotype), indicating MDGA1 is expressed presynaptically by hMCs. hMCs functionally regulate DG granule cells (GCs). To disentangle the role of MDGA1 in hMC to granule cell (GC) synaptic transmission we turned to whole cell voltage clamp of GCs. AMPAR/NMDAR excitatory postsynaptic current (EPSC) ratios (n = 7-10 cells / genotype) were significantly increased in Drd2-cre::MDGA1$^{f/f}$ mice compared to controls, while excitatory presynaptic release probability (n = 7-10 cells / genotype) and inhibitory synaptic transmission remained unchanged (n = 7-11 cells / genotype) between groups. We further wanted to

understand role of putative hMC-derived MDGA1 in multiple forms of behavioral cognition associated with hMC function. 24 hours after training between two identical objects on a novel object recognition task (NOR), control mice showed no preference between familiar and novel objects (n = 8 mice / genotype), while Drd2-cre::MDGA1$^{f/f}$ mice maintained robust discrimination (n = 10 mice / genotype). Intriguingly, Cre-positive mice expressed significant deficits in both sociability and social recognition in a three-chamber sociability task (n = 12-14 mice / genotype). Indeed, while our preliminary data is robust, the *Drd2* gene is active in a subset of interneuron subtypes within the hippocampus and cells throughout the brain. Therefore, ongoing experiments seek to enhance the regional specificity of MDGA1 deletion via virus-mediated Cre delivery into the DG. Nevertheless, our initial findings suggest a model in which removal of iML-localized MDGA1 drives enhancement of long-term novelty learning at the expense of social cognition, by unveiling monosynaptic excitatory synaptic transmission onto GCs via a trans-synaptic mechanism.

Disclosures: M.A. Sandoval: None. **M. Lu:** None. **L. Bui:** None. **J. Díaz-Alonso:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

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Program #/Poster #: PSTR083.02/J2

Topic: B.04. Synaptic Transmission

Support: -Collaborative Research Center (CRC) 1286, project A03
-Germany's Excellence Strategy–EXC 2067/1-390729940
-Research Training Group (RTG) 2824 grant "Heart & Brain diseases: integrative research across organs"

Title: Unusual long-loop recycling of synaptic adhesion and extracellular matrix proteins in hippocampal neurons

Authors: *S. HARTMANN[1], C. BOGACIU[1], S. V. GEORGIEV[1], S. RIZZOLI[1,2];
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Abstract: The formation and stability of chemical synapses rely on precise *trans*-synaptic interactions between cell-adhesion molecules (CAMs), supported by the surrounding extracellular matrix (ECM). While the functional roles of these molecules are well established, their molecular trafficking at the cellular level remains largely unknown. I analyzed here two CAMs, the presynaptic neurexin (NRXN) and the postsynaptic neuroligin (NLGN), as well as the ECM protein neurocan (NCAN). All three readily undergo endocytosis and recycling within one to three days. Colocalization analyses reveal that internalized molecules traffic through multiple intracellular compartments, including the Golgi apparatus. This finding suggests that these proteins may undergo post-translational modifications before returning to the surface. The

most probable modification in the Golgi apparatus is glycosylation. To analyze this, we combined metabolic labelling with click chemistry, to track glycan incorporation. We observed distinct glycosylation patterns for the two CAMs: NRXN2β preferentially incorporated N-Azidoacetylglucosamine (GlcNAz), whereas NLGN2 showed higher incorporation of N-azidoacetylgalactosamine (GalNAz), consistent with their known glycan modifications. For NCAN, we found enriched colocalization with GalNAz and azide-modified xyloside (XylAz), suggesting that recycling through the Golgi apparatus exposes NCAN to the glycosylation machinery within astrocytes. Overall, our results point to a recycling-based pathway in which synaptic CAMs and ECM components are continually reused. This is a starting point towards investigations on how the recycling processes may be altered in neuropsychiatric and neurodegenerative disorders.

Disclosures: S. Hartmann: None. **C. Bogaciu:** None. **S.V. Georgiev:** None. **S. Rizzoli:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

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Topic: B.04. Synaptic Transmission

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NIH Grant 1R01MH139606-01A1
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Title: High-throughput analysis of transsynaptic alignment using STED microscopy and automated synapse sorting

Authors: *A. WILTSE[1], M. DAMENTI[1], A. D. LEVY[3], A. BISWAS[5], E. MOCCI[2], S. A. AMENT[4], T. A. BLANPIED[6];
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Abstract: The strength of neurotransmission at individual synapses is critical for proper circuit function in the brain and is dysregulated in many neurological disorders. Many structural features of a synapse influence its strength, including the number of neurotransmitter release sites in the presynaptic active zone, the number and clustering of postsynaptic receptors, and the transsynaptic alignment of release sites to receptors. Thus, measurement and characterization of protein organization in the pre and postsynaptic compartments is a central goal of synapse physiology. Visualizing nanometer-scale protein organization within single synapses is challenging - diffraction-limited fluorescence microscopy methods have insufficient resolution, so super-resolution microscopy techniques are necessary. Stimulated Emission Depletion (STED) has become a reliable tool to visualize the organization of two or more proteins across

thousands of synapses given its relatively high throughput compared to other techniques, but despite these advances on the imaging front, the downstream analytical tools for this type of data are lacking. In particular, measurements of release site number and transsynaptic alignment of release sites to receptors are very sensitive to the tilt of a synapse relative to the imaging axis, forcing researchers to hand-pick en face synapses for analysis, a time-consuming process that potentially biases results. To address these challenges, we developed an automated workflow in ImageJ/FIJI for synapse detection, filtering and characterization from deconvolved two-color STED images of pre- and postsynaptic proteins in tissue. The workflow outputs lists of segmented synapses categorized by their orientation as en face, on side, or in between. By feeding the sorted synapses into downstream analyses of nanostructure and transsynaptic alignment, it then quickly and robustly reports the nano-organization of thousands of individual synapses. We demonstrated this tool by immunostaining tissue slices from mouse, rat and post-mortem human brains for pre and postsynaptic proteins and comparing their nanostructural properties across layers of cortex and cerebellum. We believe this workflow will be a valuable tool for the study of synapse nanostructure. Furthermore, the high-dimensional nanostructural datasets generated are well suited to advanced characterization of discrete and continuous axes of variation in synapse structure, and ideal accompaniment to additional data modes including spatial multiomics and calcium imaging that will yield a deep characterization of synapses across brain regions and circuits.

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Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR083.04/J4

Topic: B.04. Synaptic Transmission

Title: Revealing extracellular matrix dynamics: The interplay of tetraspanins and their interactors in ECM remodelling

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Abstract: The extracellular matrix (ECM) is a critical component of the brain, forming an intricate 3D network composed of long-lived components such as hyaluronic acid, glycoproteins, and proteoglycans. The ECM serves as a key modulator of brain homeostasis, by regulating synaptic function, stability, and long term plasticity. It is still unclear how the ECM can be remodelled on timescales compatible with dynamic neural activity. Classical ECM turnover

through proteolysis and *de novo* synthesis is unlikely to sustain rapid remodelling, suggesting that alternative mechanisms may operate at synapses. Building on our previous discovery that the ECM glycoprotein tenascin-R undergoes endocytosis and resurfacing at synapses (Dankovich *et al.*, 2021, *Nat Comm.*) , we now extend this recycling paradigm to additional ECM components and molecular regulators.
We demonstrate that the chondroitin sulphate proteoglycan neurocan (Ncan) exhibits similar recycling dynamics in neurons. Notably, we identified an unexpected role for tetraspanins in this process. Ncan recycling, which involves both glia and neurons, depends on CD81 and on its interaction partner EWI-2. Both CD81 and EWI-2 are components of tetraspanin-enriched domains, implying that tetraspanins are intimately linked to the Ncan dynamics.
To determine whether ECM recycling constitutes a universal principle, we examined additional ECM components, such as HAPLN1 (hyaluronan and proteoglycan link protein 1) and tenascin C(TNC). TNC exhibited robust recycling dynamics over three days, and its recycling appears to involve both glia and neurons, as for Ncan. In contrast, HAPLN1 underwent endocytosis, but did not reappear at the cell surface, even after prolonged periods, suggesting that this molecule is not recycled.
Together, these findings support a model in which ECM recycling and intercellular transfer of specific components, as Ncan and TNC, contribute to the dynamic maintenance of neuronal and synaptic microenvironments.

Disclosures: A. Deb: None. **S.V. Georgiev:** None. **S. Rizzoli:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

Location: WCC Halls A-C

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Program #/Poster #: PSTR083.05/J5

Topic: B.04. Synaptic Transmission

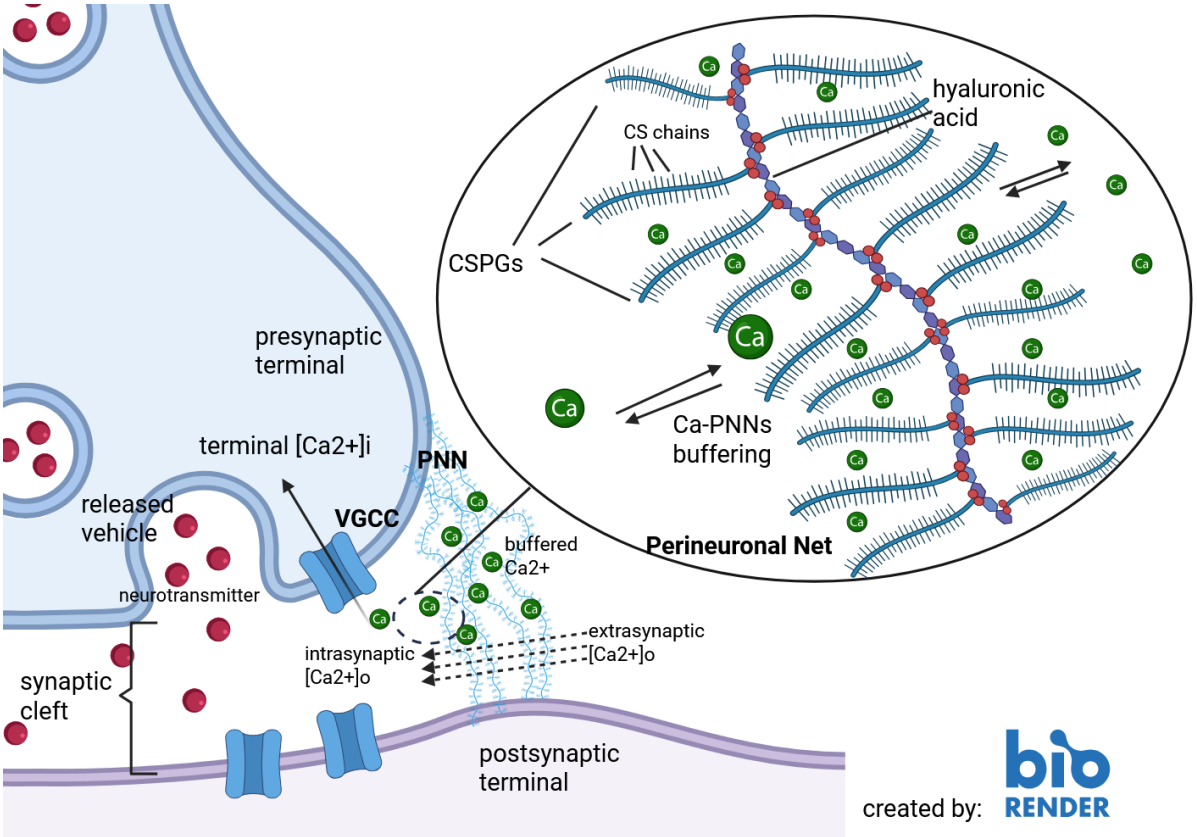
Support: 5R01NS036692-20: Role of Perineuronal Nets in Epilepsy

Title: Perineuronal Nets act as a Ca^{2+} buffer, modulating synaptic activity

Authors: *P. W. OLENIACZ[1], R. WEITZMAN[2], H. CHANDEL[2], S. ABDI[2], A. OAKLEY[3], H. SONTHEIMER[4];
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Abstract: The brain ECM accounts for ~15% of whole brain volume and consists of neuronal interstitial matrix (NIM), filling most of the extracellular space, perineuronal nets (PNNs), tightly surrounding the soma of some neurons in specific regions of the brain, and basal membrane (BM), part of the blood-brain-barrier (BBB). PNNs are particularly dense, mesh-like ECM structures of high tortuosity and highly negative charge.
PNNs are known for their modulatory effect on synaptic plasticity and neuronal excitability,

though the mechanism of action is not fully elucidated. PNNs consist of abundant chondroitin sulfate (CS) polymers attached to chondroitin sulfate proteoglycans (CSPGs) anchored on the hyaluronan backbone, and crosslinked with tenascin C, with other proteins. PNNs have been suggested to function as a selective ion diffusion barriers, based on the research focused on their Fe^{3+} binding properties. We show that PNN glycosaminoglycan compounds bind the most important signaling cations (Na^{+}, K^{+}, Ca^{2+}, and Mg^{2+}). Importantly, we detected that chondroitin sulfate, a principle building block of PNNs, binds Ca^{2+} in the presence of other signaling ions at physiological concentrations. We hypothesized that PNN-Ca^{2+} binding may regulate the availability of extracellular Ca^{2+} required for synaptic transmission. To test this hypothesis we performed classic paired-pulse experiments. We compared pair pulse responses from granule cells in the dentate gyrus in Temporal Lobe Epilepsy, which overproduce PNNs compared to granule cells in control non-epileptic brain. PNN presence correlated with obstruction of paired-pulse depression after stimulation of granule cell - medial perforant pathway synapses. The effect was mimicked by modulating extracellular Ca^{2+} concentration in normal brain. This research supports the hypothesis that PNNs' modulate synaptic activity via Ca^{2+} binding.



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Poster

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Topic: B.04. Synaptic Transmission

Support: RO1DC011099
R21NS085772
RF1MH120016

Title: Association of gap junctions and adherens junctions is widespread in electrical synapses in the Mauthner cell and zebrafish hindbrain

Authors: *O. E. TADORIAN, J. KALRA, A. E. PEREDA;
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Abstract: Most nervous systems combine electrical and chemical synapses as major modalities of neuronal communication. At chemical synapses, pre and postsynaptic compartments are organized and anchored by cell adhesion proteins that contribute to defining the synaptic boundary. In contrast, the structural and molecular organization of electrical synapses is poorly understood. Growing evidence indicates a functional interaction between the communicating mechanism of the electrical synapse, neuronal gap junctions (GJs), and cell-cell adhesion protein complexes known as adherens junctions (AJs). Recent work in our lab revealed the spatial association and distinct structural arrangement between GJs and AJs at large identifiable single mixed (electrical and chemical) synapses on the lateral dendrite of zebrafish Mauthner (M-cell) named 'Large Myelinated Club Endings' (CEs), suggesting that GJs and AJs can together be considered components of the electrical synapse at these terminals. However, it remains unclear whether this association and molecular arrangement apply to other electrical synapses of the larval zebrafish. To investigate this possibility, we used immunolabeling to explore the subsynaptic localization of GJs and AJs at synaptic inputs on various M-cell compartments and nuclei of the hindbrain. For this purpose, we immunolabeled for the neuronal GJ protein Cx35.5 (teleost homolog of mammalian Cx36) and for the cell adhesion protein ß-catenin as a marker for AJs. Confirming the widespread association between these two structures at electrical synapses, labeling for Cx35.5 and ß-catenin showed a high degree of colocalization at various synaptic inputs throughout the M-cell soma, initial segment, and ventral and lateral dendrites, as well as throughout the zebrafish hindbrain. Remarkably, as previously observed at CEs, the nanoscale resolution of expansion microscopy revealed at all contacts a notable arrangement consisting of the interleaving of ß-catenin and Cx35.5-labeled adjacent puncta. The labeled contacts show a comparable amount of labeling for both proteins, with a tendency for ß-catenin labeling to engulf the Cx35.5-labeled puncta. Thus, our data confirms the association between GJs and AJs, suggesting that they both can be considered integral components of an electrical synapse. Moreover, the association between these structures could be used as a criterion for identification of electrical synapses between neuronal processes, where delineating its boundaries is ambiguous.

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Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

Location: WCC Halls A-C

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Program #/Poster #: PSTR083.07/J7

Topic: B.04. Synaptic Transmission

Title: Dissecting the Molecular Mechanism of Rare NLGN3 Variants

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Abstract: A commonly disrupted protein network in neurodevelopmental disorders (NDDs) includes genes encoding synaptic proteins involved in functions such as synaptic adhesion (e.g., NLGNs and NRXNs), receptor localization and function, synaptic vesicle release, and postsynaptic scaffolding. In these disorders, missense mutations often impair channel or receptor activity, alter post-translational modification sites (such as phosphorylation or glycosylation), or disrupt binding interfaces. These alterations compromise the precise regulation of protein domains, affecting overall protein function and associated signaling pathways.Neuroligins (NLGNs) are postsynaptic adhesion molecules essential for neuronal development and have been implicated in NDDs. In humans, five genes encode the NLGN family of proteins. These are single-pass transmembrane proteins characterized by a large extracellular acetylcholinesterase-like domain and a short intracellular tail. NLGNs localize to the postsynaptic density, where they play a crucial role by interacting with presynaptic neurexins (NRXNs).To identify critical subdomains within the NLGN gene family, our lab developed an algorithm that evaluates tolerance to missense mutations by comparing clinical variants from ClinVar with reference variants from gnomAD. Using this approach, we identified a cluster of four NLGN3 variants associated with NDDs. One variant, V204A, was found in 27 out of 108 children diagnosed with autism spectrum disorder. Our studies indicate that two of the four identified variants result in trafficking deficits when expressed in HEK cells. Notably, the NLGN3 V204F and V204A variants exhibit impaired maturation and increased endoplasmic reticulum (ER) retention. When expressed in HeLa cells, these variants also show impaired surface trafficking.Ongoing studies are assessing trafficking and synapse localization in neurons as well as binding to presynaptic NRXNs. These investigations will provide further insight into the mechanisms of neuronal dysfunction observed in patients with rare variants in this newly identified cluster.

Disclosures: K. Hossain: None. **T. Do:** None. **A.W. Lehr:** None. **K.W. Roche:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

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Program #/Poster #: PSTR083.08/J8

Topic: B.04. Synaptic Transmission

Support: 1ZIANS003140

Title: The neuroligin-3 intracellular domain regulates transcription and promotes glioma growth

Authors: *K. F. MCDANIEL[1], T. H. DO[1], E. HONG[1], Y. BANASAVADI SIDDEGOWDA[2], K. W. ROCHE[1];
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Abstract: Neuroligins (NLGNs) are a family of post-synaptic single-pass transmembrane proteins that bind trans-synaptically to neurexins to enable the formation and maintenance of synapses. NLGN3, specifically, is localized to both excitatory and inhibitory synapses and is implicated in the pathologies of neurodevelopmental disorders and glioma. Specifically, NLGN3 undergoes proteolytic cleavage to produce a soluble ecto-domain (ECD) that is known to increase glioma proliferation. However, there is a remaining cellular C-terminal fragment (CTF) of NLGN3 following ECD cleavage that has yet to be investigated. Here, we characterized the cleavage and trafficking pathways of the NLGN3 CTF to determine the downstream intracellular effects of NLGN3 proteolytic cleavage. Following cleavage of the full-length protein, the NLGN3 CTF undergoes a second cleavage event mediated by gamma-secretase that results in a soluble intracellular domain (ICD). Strikingly, we find that the NLGN3 ICD translocates to the nucleus and regulates gene transcription. We discovered that the NLGN3 ICD up-regulates expression of the Rho-GTPase activating protein ARHGAP30, a known glioma mitogen. We find that expression of the NLGN3 ICD in U87 glioma cells increases ARHGAP30 message. Further, we find that the NLGN3 ICD, in a domain-specific manner, increases proliferation and migration in U87 cells. Overall, our data establishes a vital and unexpected role for the NLGN3 ICD as a regulator of transcription and a mitogenic factor promoting glioma growth.

Disclosures: K.F. McDaniel: None. **T.H. Do:** None. **E. Hong:** None. **Y. Banasavadi siddegowda:** None. **K.W. Roche:** None.

Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

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Program #/Poster #: PSTR083.09/K1

Topic: B.04. Synaptic Transmission

Support: SMART D2403012
NSFC82350710225

Title: Thalamic ephrinB-EphBreceptorsignalingactivation inemergence fromanesthesia

Authors: Y. LIU[1], J. HU[1], B. CAO[1], H. YAO[1], ***P. CHEN**[2,1], X.-J. SONG[1];
[1]Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Shanghai Med. College, Fudan Univ., Shanghai, China

Abstract: Emergence from anesthesia was assumed to be a reverse process of induction of anesthesia and depend on the elimination of the anesthetic from the body. There are indications, however, that the relationship between the two processes is more complex than initially appreciated. We have recently demonstrated that emergence of consciousness from anesthesia is orchestrated by an intrinsic driving force in the brain. Ubiquitin degradation of potassium-chloride co-transporter 2 (KCC2) in the ventral posteromedial nucleus (VPM) of the thalamus plays a critical role in the emergence from anesthesia. Here, we further show in mice that, when the brain is in a minimal responsive state by an anesthetic, the ephrinB-EphB1 receptor signaling was activated in the VPM and the primary somatosensory cortex (S1), contributing to the emergence of consciousness from anesthesia. Activation of ephrinB-EphB1 receptor signaling excites glutamatergic neurons in the VPM through phosphorylation of NR2B at tyrosine-1472 and disinhibits VPM neurons through ubiquitin degradation of KCC2. In addition, we observed that anesthetized animals exhibited sustained seizure-like tremors in their forelimbs, typically beginning after 60 min (at the verge of exit from the deep anesthesia) and lasting for about 10-40 min before the recovery from loss of consciousness. We speculate that activation of ephrinB-EphB receptor signaling induced excitation and KCC2 degradation-induced disinhibition of neurons may contribute to such anesthetic epilepsy. Meanwhile, the ephrinB-EphB1 receptor signaling was also activated in the spinal dorsal horn, contributing to the decreased threshold of withdrawal response to the peripheral stimulation.Taken together, the EphB1/NR2B and EphB1/KCC2 signaling pathways in the VPM are two independent mechanisms in the process of emergence from anesthesia. Activation of the EphB1/NR2B excites VPM neurons, and KCC2 down-regulation disinhibits the VPMGlu neurons, both accelerating recovery of the VPM-S1 pathway activity and consciousness from anesthetic inhibition.This study provides further insights into understanding the molecular and neural circuit basis for the brain to emerge from anesthesia.

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Poster

PSTR083: Transynaptic Structure and Extracellular Dynamics

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Program #/Poster #: PSTR083.10/K2

Topic: B.04. Synaptic Transmission

Support: NIH grant 5R01NS125359-04

Title: Mechanistic Studies of NRAP-1, a Presynaptic Modifier of Synaptic Strength

Authors: *G. M. SAPP[1], J. E. MELLEM[1], D. MADSEN[1], A. V. MARICQ[2];
[1]Neurobio., Univ. of Utah, Salt Lake City, UT; [2]Neurobio., Univ. of Utah, Salt Lake Cty, UT

Abstract: Synaptic strength depends on the number of functional postsynaptic receptors that can respond to released neurotransmitters. Here I investigated NRAP-1, a presynaptically secreted protein in *C. elegans* that functions as an auxiliary protein required for the activity of postsynaptic NMDA-type ionotropic glutamate receptors (NMDARs). Given the established role of NMDARs in synaptic plasticity, NRAP-1 may contribute to activity-dependent modulation of synaptic strength. However, despite recent advances in understanding the role of NRAP-1 in NMDAR function, the cellular mechanisms that govern its trafficking and release and whether this release is activity dependent remain unknown. To address these questions, I utilized *in vivo* imaging in conjunction with electrophysiological analysis. For imaging studies, I generated transgenic *C. elegans* that express a functional NRAP-1 tagged with Green Fluorescent Protein (GFP) to monitor the transport and localization of NRAP-1 in neuronal processes. In parallel, whole-cell patch-clamp electrophysiology was used to measure membrane currents, elicited by pressure application of 1mM NMDA, from the AVA interneuron. All worms were age-synchronized young adult hermaphrodites. Confocal imaging of transgenic worms demonstrated that NRAP-1 localizes to puncta along the neuronal process and undergoes processive movement at a velocity of ~ 1.3 μm/s (n = 4), consistent with motor-mediated transport. Preliminary electrophysiological recordings from *unc-31* mutants (lacking the CAPS protein that is required for release of dense-core vesicles) revealed no appreciable difference in NMDAR currents compared to controls, consistent with NRAP-1 release occurring through a mechanism independent of canonical DCV-dependent neuropeptide secretion. Together, these exploratory findings suggest that NRAP-1 may not behave as a classical neuropeptide and instead may utilize distinct trafficking and release mechanisms. NRAP-1 represents a previously unrecognized presynaptic mechanism for controlling postsynaptic NMDAR activation competence, revealing a new regulatory layer in excitatory neurotransmission. By uncovering the principles that govern NRAP-1 trafficking and secretion, this research will open new directions for exploring whether analogous presynaptic regulatory pathways operate in mammalian systems and contribute to neuronal communication and synaptic strength.

Disclosures: G.M. Sapp: None. **J.E. Mellem:** None. **D. Madsen:** None. **A.V. Maricq:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

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Program #/Poster #: PSTR084.01/K3

Topic: B.05. Synaptic Plasticity

Support: IBS-R001-D3

Title: Protein synthesis-dependent engram synapse strengthening underlies fear memory reactivation

Authors: *H. LEE[1], I. HONG[2], Y. KIM[4], H. JUNG[2], C.-H. KIM[5], J.-H. CHO[6], B.-K. KAANG[3];
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Abstract: Memory is thought to be stored within neuronal ensembles known as engram cells, yet how changes at the synaptic level contribute to engram function remains incompletely understood. To investigate this relationship, we employed the dual-eGRASP technique to visualize synaptic connections between ventral CA1 and basal amygdala neurons during contextual fear memory formation in mice. Contextual fear conditioning increased the density of connections between engram cells and promoted structural enhancement of these synapses, suggesting a critical role for engram-specific synaptic plasticity in memory storage. We further examined the contribution of protein synthesis using anisomycin-induced amnesia. Mice receiving a single anisomycin injection retained optogenetically evoked fear responses despite impaired natural memory recall, whereas mice treated repeatedly with anisomycin over six hours exhibited deficits in both natural and optogenetically induced memory retrieval. Synaptic analyses revealed that a single anisomycin treatment reduced engram spine size without affecting engram synapse density, while repeated treatment caused reductions in both measures. These findings demonstrate that protein synthesis is necessary for maintaining the structural integrity of engram synapses and that disruption of engram synapse density and morphology is closely associated with impaired fear memory retrieval.

Disclosures: H. Lee: None. **I. Hong:** None. **Y. Kim:** None. **H. Jung:** None. **C. Kim:** None. **J. Cho:** None. **B. Kaang:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.02/K4

Topic: B.05. Synaptic Plasticity

Title: SnRNA-Seq Reveals Synaptic Differences Between Susceptible and Resilient Mice After Chronic Traumatic Exposure

Authors: *D. JEAN[1], Y. LI[2];
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Abstract: The neural mechanisms underlying stress-induced psychiatric disorders such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) remain poorly understood. These challenges stem partly from the complexity of investigating these disorders and the heterogeneity of individual responses to chronic stress. This present study examines the molecular mechanisms that distinguish resilient and susceptible responses to chronic stress. Male C57BL/6J mice underwent a 10-day chronic social defeat stress (CSDS) paradigm and were

classified as either resilient or susceptible based on measures of social avoidance. The medial prefrontal cortex (mPFC) was then collected from naïve, resilient, and susceptible mice for single-nucleus RNA sequencing analysis. After cell clustering and pathway analysis, a significant portion of cells were identified as excitatory neurons with synaptic gene pathways being inversely regulated between susceptible and resilient groups. Based on differentially expressed synaptic genes, a working model was constructed to proposed for the molecular mechanisms that differentiate susceptible and resilient behavioral phenotypes. These findings highlight the molecular underpinnings that contribute to resilience in psychiatric disorders, such as PTSD and MDD. A deeper understanding of resilience to chronic stress may facilitate the development of novel treatments and provide insights into the molecular pathways involved in stress-induced disorders.

Disclosures: D. Jean: None. **Y. Li:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.03/K5

Topic: B.05. Synaptic Plasticity

Title: Single-nucleus transcriptomics reveals time-dependent and cell type-specific effects of psilocybin and ketamine on gene expression

Authors: *A. M. WEINER[1], C. LIAO[2], N. K. SAVALIA[2], M. J. GIRGENTI[3], K. Y.-C. KWAN[4], A. KWAN[1];
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Abstract: There is growing interest to investigate classic psychedelics and ketamine as therapeutics for mental illnesses. Previous studies have demonstrated that one dose of psilocybin or ketamine leads to persisting neural and behavioral changes. The durability of these effects suggests that there are likely alterations of gene expression at the transcriptional level. In this study, we performed single-nucleus RNA sequencing of the dorsal medial frontal cortex of male and female mice. Samples were collected at 1, 2, 4, 24, or 72 hours after psilocybin or ketamine administration and from control animals. At baseline, major subtypes of excitatory and GABAergic neurons selectively express particular serotonin receptor transcripts. The psilocybin-evoked differentially expressed genes in excitatory neurons were involved in synaptic plasticity, distinct from genes enriched in GABAergic neurons, which contribute to mitochondrial function and cellular metabolism, and non-neuronal glial cells. The effect of psilocybin on gene expression was time-dependent, including an early phase at 1 hour followed by a late phase at 72 hours of transcriptional response after administration, which differs from the peak changes at 2 - 4 hours following ketamine administration. Collectively, the results provide a resource for

understanding the cell type-specific and time-dependent changes in gene expression induced by psilocybin and ketamine in the mouse medial frontal cortex, which may underpin the drug's long-term effects on neural circuits and behavior.

Disclosures: A.M. Weiner: None. **C. Liao:** None. **N.K. Savalia:** None. **M.J. Girgenti:** None. **K.Y. Kwan:** None. **A. Kwan:** 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.; Intra-Cellular Therapies. Other; Boehringer Ingelheim, Eli Lilly, Empyrean Neuroscience, Freedom Biosciences, Helus Pharma, Otsuka, Xylo Bio.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.04/K6

Topic: B.05. Synaptic Plasticity

Title: Distinct miRNA-mediated Epigenetic Regulation of Synaptic Genes in Medulloblastoma and Diffuse Midline Glioma

Authors: *M. SEBLANI[1], K. COLEMAN[2,1], B. SONG[3], J. ROKITA[2], D. HAYDAR[2]; [1]Children's Natl. Hosp., Washington, DC; [2]Washington, DC, ; [3]Children's Natl. Med. Ctr., Washington, DC.

Abstract: Brain tumors are among the most common solid malignancies in children and are associated with high and early mortality. They are classified in distinct groups based on anatomical, histological, cellular and molecular criteria. Advances in molecular genetics have confirmed the critical role of microRNAs (miRNA) in neuro-oncogenesis and in the development and progression of the disease. However, miRNA's role in modulating neuronal identity and synaptic functions in brain tumor cells remains poorly understood. Here, we performed small RNA sequencing and bulk RNA sequencing on control brain tissues and patient-derived tumors from medulloblastoma (MB) and diffuse midline glioma (DMG). Our data showed that several miRNAs, including hsa-miR-193a-5p and hsa-miR-892b in DMG and novelmiRNA-2872 and novelmiRNA-3342 in MB, showed broad enrichment across multiple neuronal pathways. Gene set variation analysis revealed that specific clusters of differentially expressed miRNAs in MB and DMG are negatively correlated with synaptic and neuronal pathways. Significant negative correlations between differentially expressed miRNAs and their predicted target genes as well as transcriptomic changes of genes encoding synaptic machinery components, indicate a role for these miRNAs in modulating neuronal functions in tumor cells and forcing a developmental-like cellular state. Interestingly, MB showed a broader range of downregulated target genes compared to DMG which indicates differences in neuronal differentiation programs in these two groups. Notably, DMG show upregulation of AMPA glutamatergic receptor and a repression of GABA(B) but not GABA(A) subunit receptors. MB

showed less selective global repression with few upregulated genes encoding for Glycine and Glutamate signaling machinery involved in the survival of early-stage neural progenitors. Together, these findings show the contribution of neurofunctional program modulation in oncogenesis and provide a framework to understand the distinct tumor to neuron interactions observed in DMG versus MB. They also suggest the existence of predictive neuronal molecular programs that capture tumor neuro-microenvironment dynamics across pediatric brain tumors.

Disclosures: M. Seblani: None. **K. Coleman:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.05/K7

Topic: B.05. Synaptic Plasticity

Support: CHRI-Rowan-Dept. BMS

Title: Electroconvulsive shock and ketamine differentially affect cell type-specific gene transcription in mouse hippocampus

Authors: *T. N. FERRARO[1], B. C. REINER[2], S. NASSER CHEHIMI[3], T. M. KECK[5], R. J. BUONO[1], R. CRIST[4];
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Abstract: Electroconvulsive shock (ECS) and ketamine (KET) are both used to achieve rapid antidepressant effects in patients with treatment-resistant depression; however, the extent to which these treatments engage similar brain mechanisms is unclear. To gain new insight, we treated male C57BL/6J mice with ECS (3 seizures spaced 15 min apart) or racemic KET (10 mg/kg, i.p.) and euthanized them 1 or 24 h later. We gave control mice sham ECS or an i.p. vehicle injection. We conducted snRNA-seq on hippocampus using 10x Genomics methodology, clustered 21 cell types (15 neuronal subtypes) and analyzed data with Seurat and Libra to find differentially expressed genes (DEGs). We analyzed DEGs with Gene Ontology (GO), functional mapping of genetic association studies (FUMA) and ingenuity pathway analysis (IPA) to identify cell type-specific phenotypes related to treatments. One hour following ECS, we found a total of 10,775 DEGs, 10,538 of which were in 3 subtypes of dentate gyrus granule cells (GCs). At 24 h, we found a total of 899 DEGs distributed mainly between GCs (N=272), CA1 neurons (N=394) and CA3 neurons (N=127). Pathway analyses reveal that striking ECS effects at 1 h are mediated by major transcription factors including Arc and Creb. At 24 h, changes are observed in many neurotransmitter and hormone systems and second messenger pathways. One hour following KET, we found only 47 DEGs, the largest number in CA1 neurons (N=16). However, pathway analysis shows this group of genes is significantly enriched for genes

involved in glutamate neurotransmission. At 24 h, we found a total of 575 DEGs; however, only a small number are in CA1 neurons (N=18) with many more (N=534) in neurons from the subiculum and entorhinal cortex. Pathway analyses reveal a much broader set of functional effects of KET 24 h following treatment including strong impact on glutamatergic and opioidergic systems. At 24 h, both ECS and KET impact pathways related to neuroplasticity including axon guidance, dendritic sprouting, synaptic development and neurogenesis. In summary, ECS causes major alteration of the hippocampal transcriptome, primarily impacting dentate gyrus GCs at 1 h, with effects extending to include CA3 and CA1 neurons at 24 h. KET has a more limited impact on the hippocampal transcriptome, especially at 1 h where its effects may be limited to CA1 neurons; however, at 24 h, KET significantly alters gene expression in entorhinal cortex neurons that project to dentate gyrus GCs and in CA1 and subiculum neurons that project out of the hippocampus. Refined integration of effects at early and late time points will allow formulation of testable hypotheses regarding shared and distinct actions of ECS and KET.

Disclosures: T.N. Ferraro: None. **B.C. Reiner:** None. **S. Nasser Chehimi:** None. **T.M. Keck:** None. **R.J. Buono:** None. **R. Crist:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.06/K8

Topic: B.05. Synaptic Plasticity

Support: F31NS137619
R01MH128199

Title: A noncanonical role for NFAT signaling during inhibitory synaptic plasticity

Authors: *S. WOLFE[1], K. HAHM[2], J. D. GARCIA[3], M. L. DELL'ACQUA[4], K. R. SMITH[5]; [1]Univ. of Colorado Anschutz Med. Campus, Denver, CO; [2]Univ. of Colorado Anschutz Med. Campus, Aurora, CO; [3]Ctr. for Integrative Neurosci., The Univ. of California, San Francisco, San Francisco, CA; [4]Dept.Pharmacology, Univ. Colorado Sch. of Med., Aurora, CO; [5]Pharmacol., Univ. of Colorado, Aurora, CO

Abstract: Inhibitory synapses undergo many forms of bidirectional plasticity which controls various forms of learning, memory, and cognition. During inhibitory long-term potentiation (iLTP), *de novo* synthesis of inhibitory synaptic proteins sustains long-term changes in synaptic strength. We have found that microRNAs (miRNAs), miR376c and miR153, repress translation of key $GABA_A$ receptor ($GABA_AR$) subunits and the inhibitory synaptic scaffold, gephyrin. Following iLTP induction, the transcription of these miRNAs is repressed, reducing miRNA levels and enabling increased translation of their targets, $GABA_ARs$ and gephyrin. We find that the activity-dependent transcription factor, NFAT, is a major repressor of miRNA transcription

during iLTP. Here, I will show that NFAT activity is required for inhibitory synaptic potentiation and identify the upstream signaling mechanisms that are crucial in mediating excitation-transcription coupling during inhibitory synaptic plasticity.

Disclosures: S. Wolfe: None. **K. Hahm:** None. **J.D. Garcia:** None. **M.L. Dell'Acqua:** None. **K.R. Smith:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.07/L1

Topic: B.05. Synaptic Plasticity

Support: NIH Grant U54MD007600
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Seed Funds from the UPRCa Deanship of Academic Affairs

Title: Sex-Dependent Behavioral and Molecular Alterations in Adult Offspring Following Prenatal Restraint Stress: Implications for Oxidative Stress and Neuronal Plasticity

Authors: *S. I. TORRES[1], E. J. CRUET-ORTIZ[2], Z. MARRERO-COSME[3], G. A. ROBLES GUZMÁN[3], E. RUIZ-FÉLIX[3], N. VALENTIN-MITI[2], C. E. MARÍA-RÍOS[4], C. BRAVO-RIVERA[5], J. M. SANTIAGO SANTANA[2], Y. ARROYO[6];
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Abstract: Prenatal stress (PNS) has been associated with long-term neurobiological alterations that affectemotional regulation, motivation, and cognitive function. Approximately 40% of pregnant womenexperience significant stress during gestation, potentially disrupting fetal brain developmentthrough mechanisms involving neuroinflammation and oxidative stress. The aim of this study wasto evaluate the behavioral and molecular consequences of PNS in the offspring of mothers exposedto prenatal stress. We hypothesized that PNS exposure would induce changes at the behavioral andmolecular levels. Pregnant dams were subjected to a two-week restraint stress protocol during lategestation and were divided into stressed (PNS) and non-stressed (control) groups. Adult offspringwere evaluated through several behavioral tests, such as social interaction, and platform-mediatedavoidance tasks. Brain homogenates from different regions such as midbrain and pre-frontal cortexwas analyzed using Western blot to quantify the expression of GAP-43 and Catalase. Behavioralanalyses revealed sex-dependent differences between groups. PNS-exposed males displayedreduced social interaction toward mothers and opposite-sex individuals. Females in theexperimental group (PNS-exposed) showed a significant

reduction in locomotor activity andCatalase expression in the prefrontal cortex, suggesting an increased vulnerability to oxidativestress accumulation in this region. Analyses of midbrain revealed significant changes in GAP-43expression, suggesting potential alterations in neuronal plasticity and axonal growth processesassociated with prenatal stress. Our findings support our hypothesis that PNS exposure promotesboth behavioral and molecular alterations. Our results suggest that males born to mothers exposedto PNS may be more prone to developing antisocial behaviors toward opposite-sex individuals.Conversely, females from PNS-exposed mothers tended to display greater anxiety-like or nervousbehavior and appeared to be more vulnerable than males to the accumulation of reactive oxygenspecies. Future studies will continue investigating molecular alterations associated with postnatalstress to further understand how these mechanisms contribute to the neurobiological changesobserved.

Disclosures: S.I. Torres: None. **E.J. Cruet-Ortiz:** None. **Z. Marrero-Cosme:** None. **G.A. Robles Guzmán:** None. **E. Ruiz-Félix:** None. **N. Valentin-Miti:** None. **C.E. María-Ríos:** None. **C. Bravo-Rivera:** None. **J.M. Santiago Santana:** None. **Y. Arroyo:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.08/L2

Topic: B.05. Synaptic Plasticity

Support: FRAXA Research Foundation Fellowship
Reeve-Irvine Research Center

Title: Spatial transcriptomics screening identifies candidate activity-dependent dendritic transcripts and altered transcript localization in Fmr1 KO mice

Authors: *P. S. PIRBHOY[1], O. STEWARD[2];
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Abstract: Synaptic plasticity depends on coordinated synthesis, delivery, and translation of mRNAs. The immediate early gene Activity-regulated Cytoskeletal-associated protein/Arg3.1 (Arc) is rapidly targeted to dendrites following synaptic activity and learning and serves as a model for activity-dependent mRNA localization. Few transcripts have been shown to exhibit such rapid, activity-dependent dendritic localization. Here, we undertake an initial screen for transcripts exhibiting activity-dependent localization using the 10x Genomics Xenium platform, which targets 247 genes. To accomplish this, mice were subjected to one of two well-characterized conditions known to induce Arc localization in hippocampal dendrites: (1) electroconvulsive seizure (ECS); (2) 1 h of unsupervised learning in a toy-filled enriched environment. Mice were euthanized either 2 h after ECS, after 1 h of unsupervised learning, or directly from their home cage as controls. We also assessed whether dendritic localization of Arc

mRNA was altered in mice lacking the mRNA binding protein Fragile X messenger ribonucleoprotein 1 (*Fmr1* KO mice). Transcript distribution was analyzed across cell body and dendritic laminae in coronal sections of the dorsal hippocampus using the Xenium platform. Confirming previous studies, ECS robustly induced Arc transcription in dentate granule cells and markedly increased Arc mRNA levels within dendritic laminae. Similarly, as previously reported, 1 h of exploration in an enriched environment activated Arc transcription in CA1 neurons. Region-of-interest analysis in the dentate gyrus and CA1 identified additional transcripts including Cabp7, Gfap, Kctd12, and Slc17a7 that exhibited layer-specific enrichment following activity. *Fmr1* KO mice exposed to the enriched environment displayed comparable levels of Arc expression as WTs. Interestingly, Arc localization across CA1 basal and apical dendritic compartments was altered despite comparable Arc induction. Together, these findings confirm Arc as the most robust activity-dependent dendritic transcript detected in the Xenium panel while identifying additional transcripts with region- and layer-specific enrichment and suggesting that FMRP contributes to activity-dependent mRNA localization.

Disclosures: P.S. Pirbhoy: None. **O. Steward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); OS is a co-founder, and has economic interests in the company Axonis Inc., which is developing novel therapies for neurological disorders..

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.09/L3

Topic: B.05. Synaptic Plasticity

Support: AWD0012573: HFSP - Jonas 06/01/2024

Title: Long Term Potentiation Triggers Sequential Waves of Local Translation for Synaptic Remodelling and Metabolic Adaptation

Authors: *B. PETRITI[1], P. LICZNERSKI[2], S. SUBRAMANIAN[4], L. SHEN[3], E. A. JONAS[5]; [2]Intrnl. Medicine/Section Endocrinol., [1]Yale Univ., New Haven, CT; [3]Intrnl. Med., Yale Univ., Wallingford, CT; [4]Yale Univ. Sch. Med., New Haven, CT; [5]Yale Univ. Sch. Med., Hamden, CT

Abstract: Localized protein synthesis within the synaptic terminal is essential for fuelling structural and functional plasticity during long-term potentiation (LTP). However, the precise temporal orchestration of local translation and its coupling to synaptic energy demands remain poorly defined. Using quantitative proteomic profiling of isolated synaptosomes, we identified changes in proteins involved in mitochondrial metabolism and synaptic function. We track a highly coordinated, time-dependent wave of local protein synthesis following LTP induction. At the immediate 30-minute post-LTP mark, canonical translation initiation machinery is globally suppressed; yet the synaptosome executes an autonomous, cap-independent "fast-response"

program. This initial phase selectively synthesizes elite bioenergetic control nodes to immediately tune existing mitochondrial electron transport chain (ETC) coupling efficiency, coinciding with a rapid priming of upstream glycolysis. Moreover, it occurs in tandem with an early-phase mobilization of select synaptic vesicle and signalling proteins, establishing the necessary conditions for subsequent morphological remodelling. By 60 minutes, a translational shift occurs, marked by the widespread recruitment of specialized ribosomal complexes and RNA-binding chaperones. This peak in the translational machinery drives an intensive upregulation of the entire cytosolic glycolytic cascade and Krebs cycle enzymes to process the sudden influx of metabolic substrate, which is synchronized with the synthesis of core cytoskeletal actin and microtubule-organizing proteins, required for synaptic remodelling.Finally, at 120 minutes, this cytosolic translation wave recedes slightly as the terminal transitions to a mature state dedicated to the localized refinement of mitochondrial and synaptic architecture. Together, these findings reveal a sophisticated, hierarchical tier system where the synapse reconfigures its local proteome to sustain the high energetic costs of synaptic plasticity.

Disclosures: B. Petriti: None. **P. Licznerski:** None. **S. Subramanian:** None. **L. Shen:** None. **E.A. Jonas:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.10/L4

Topic: B.05. Synaptic Plasticity

Support: NIH K25CA270079
NSF 2341725
NSF CAREER 2443386
NIH P20GM162339
BIC 2.0 OU
OU DISC NEXUS

Title: Cellular and Molecular Profiling of the Inferior Colliculus

Authors: *M. R. MOUSSA[1], A. L. BURGHARD[2];
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Abstract: Auditory pathologies, especially hearing loss, are associated with poor cognitive function, problems in communication, and reduced social engagement. Studying the mechanisms of the central auditory system is vital in understanding hearing disabilities and its correlation with other sensory impairments. The Inferior Colliculus (IC) brain region is responsible for sound localization and sound mapping. The inferior colliculus (IC) is a major hub in the central

auditory system. It has been the focus of decades of research, however much of its local circuitry remains incompletely understood. One reason is the lack of specific molecular markers for the different neuron population present in the IC. While neuron types have been differentiated by morphology, neurotransmitter or intrinsic membrane properties, most studies only combined two of these categories to describe a cell type, e.g. the categorization of GABA cells into small and large. Only few studies have been able to consolidate several aspects of neuron classification and identified specific molecular markers for the IC cell types.In this study, we utilize single nuclei sequencing technologies to establish a complete cellular profile of neurons in the IC. We examined the transcriptomic profiles of the IC cell types and compared gene expression changes variations in the IC of CBA/CaJ mice of both sexes between sound-exposed and control mice. We sequenced gene expression profiles of ~7200 nuclei and used advanced computational approaches to identify 16 neuronal and non-neuronal cell populations and multiple subpopulations with distinct transcriptomic profiles, elucidating the composition of the IC in terms of cell and functional types.

Disclosures: M.R. Moussa: None. **A.L. Burghard:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.11/L5

Topic: B.05. Synaptic Plasticity

Title: pDANCE: A Bayesian Framework for Measuring Synaptic Protein Turnover In Vivo

Authors: *Y.-Z. WANG[1], J. N. SAVAS[2];
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Abstract: Protein turnover, defined as the balance between synthesis and degradation, is a fundamental in vivo metric of protein behavior that is orthogonal to expression abundance. Pulsed stable isotope labeling in mammals (pSILAM) coupled with mass spectrometry (MS) enables quantitative protein turnover measurements. Computational methods infer protein lifetimes from time-resolved heavy-label incorporation, informing dynamic processes such as learning/memory and supporting therapeutic target discovery in neurodegenerative and neurodevelopmental disorders. However, conventional pulsed-labeling workflows rely on steady-state assumptions, including constant total protein abundance and fixed synthesis and degradation rates. These assumptions frequently do not hold in the brain. We therefore developed protein Dynamics and Computational Estimation (pDANCE), a framework that precisely infers protein turnover kinetics from pulsed SILAM-MS data in non-steady-state systems.
pDANCE is a GPU-accelerated, hierarchical Bayesian framework for inferring protein turnover kinetics from pulsed SILAM-MS data without assuming steady state. pDANCE models time-varying synthesis and degradation through a mechanistic delayed-differential-equation (DDE)

formulation that links heavy-label uptake to protein pool dynamics, while accounting for batch and mouse effects via hierarchical priors. Using Hamiltonian Monte Carlo with optional variational warm starts, pDANCE jointly estimates posterior distributions for protein-specific kinetic parameters and provides uncertainty-aware half-life and lifetime summaries. This enables robust turnover inference during dynamic biological states, including brain development, activity-dependent synaptic remodeling, and disease contexts in which protein dynamics are perturbed, such as Alzheimer's disease and autism spectrum disorder.

Disclosures: Y. Wang: None. **J.N. Savas:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.12/L6

Topic: B.05. Synaptic Plasticity

Support: R01 MH116900

Title: Quinone reductase 2 reads H3 serotonylation to support neuronal maturation

Authors: *M. CHEN[1], I. S. MAZE[2];
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Abstract: Histone H3 Gln5 serotonylation (H3Q5ser) is a recently described posttranslational modification[1] that plays important roles in guiding transcriptional permissiveness in brain and peripheral systems. H3Q5ser has been implicated in diverse physiological and pathological processes ranging from neural differentiation to sensory processing, circadian rhythmicity, stress responsivity, placental gene regulation, and tumorigenesis. Since H3Q5ser can occur in combination with H3 Lys4 trimethylation (H3K4me3), most mechanistic studies to date have focused on H3Q5ser's roles in modulating H3K4me3 *reader* interactions, where it has been shown to potentiate TAF3/TFIID binding to H3K4me3 and inhibit the recruitment of K4me3 demethylases; however, whether H3 serotonylation functions as an autonomous chromatin signaling mark through dedicated *reader* proteins has remained unknown. Here, using a combination of proteomic-, structural-, molecular-, epigenomic-, and cellular-based approaches, we demonstrate that the Quinone reductase 2 (QR2) enzyme *reads* H3Q5ser independently of H3K4me3. CRISPR-Cas9-mediated disruption of H3 serotonylation or QR2's binding to the mark in human induced pluripotent stem cell-derived neurons impairs the establishment of neuronal transcriptional programs, alters synaptic connectivity, and disrupts electrophysiological maturation. These findings thus uncover an H3 serotonylation-dependent chromatin signaling axis that is essential for human neurodevelopment.

Disclosures: M. Chen: None. **I.S. Maze:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

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Program #/Poster #: PSTR084.13/L7

Topic: B.05. Synaptic Plasticity

Support: 5R01NS057819

Title: Presymptomatic training restores experience-dependent transcriptional programs underlying synaptic plasticity and learning in a Rett syndrome mouse model

Authors: *Y. LI[1], H. Y. ZOGHBI[2];
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Abstract: Rett syndrome (RTT), caused by loss-of-function mutations in *MECP2*, is characterized by apparently normal early development followed by neurological regression. Presymptomatic behavioral training substantially improves motor and cognitive function in RTT mouse models, yet the cellular and transcriptional mechanisms underlying this timing dependence remain unknown. Here, we combined FosTRAP-INTACT labeling with single-nucleus RNA sequencing (snRNA-seq) to profile transcriptional states in task-activated hippocampal neurons from behaviorally characterized mosaic *Mecp2*$^{+/-}$ mice. This approach enabled direct comparison of training-induced transcriptional responses in the same neurons whose activity was captured during learning. We first defined a cell-type-specific disease signature in the RTT hippocampus. Both presymptomatic and symptomatic training partially reversed disease-associated transcriptional changes across multiple cell types, demonstrating that behavioral experience can engage transcriptional recovery even in the symptomatic brain. However, only presymptomatic training restored immediate early gene (IEG) transcriptional homeostasis in dentate gyrus (DG) granule neurons. In untrained and post-symptomatically trained RTT mice, IEGs including *Fos*, *Fosb*, *Jun*, *Arc*, and *Npas4* remained elevated 10 days post-training which is a pattern reflecting failed transcriptional silencing after learning. Presymptomatic training selectively normalized this aberrant IEG expression, indicating that MeCP2 is required for activity-dependent transcriptional resetting following experience. In parallel, presymptomatic training preferentially normalized gene programs associated with synaptic organization and membrane-potential regulation in inhibitory interneurons, with prominent effects in PV/SST- and Chrm2-expressing populations. Consistent with this, cell-cell communication analyses revealed disrupted NRG1-ErbB4 signaling to Chrm2-expressing interneurons in RTT, which was selectively normalized by presymptomatic but not post-symptomatic training. Together, these findings suggest MeCP2 is required for experience-dependent transcriptional resetting after learning and define a presymptomatic window during which this capacity can be rescued.

Disclosures: Y. Li: None. **H.Y. Zoghbi:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.14/L8

Topic: B.05. Synaptic Plasticity

Support: 5R01MH116900-08

Title: Ketamine Induces a Sustained Increase in Histone H3 Serotonylation that Outlasts Its Acute Transcriptional Wave in the mPFC

Authors: *Y. SONG[1], G. DI SALVO[3], B. WEEKLEY[2], I. S. MAZE[4,5];
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Abstract: While ketamine has emerged as a breakthrough treatment for treatment-resistant depression (TRD) due to its rapid and sustained efficacy, the precise epigenetic mechanisms governing its long-term impact on gene expression remain unclear. Recent evidence demonstrates that histone H3 serotonylation (H3K4me3Q5ser), a transcriptionally permissive chromatin mark, is dysregulated in the dorsal raphe nucleus (DRN) in chronically stressed mice and major depressive disorder (MDD) patients, a pathology that is reversed by chronic fluoxetine treatment. Given that ketamine's antidepressant efficacy requires serotonergic recruitment within the medial prefrontal cortex (mPFC), we investigated its impact on H3K4me3Q5ser dynamics and the transcriptome within the mouse mPFC across a temporal window (1h, 24h, and 72h post-treatment) utilizing CUT&RUN and RNA sequencing. Here, we report that a single, subanesthetic dose of ketamine induces a genome-wide increase in H3K4me3Q5ser at 24h that persists through the 72h timepoint. Differential peak analysis revealed a dominance of upregulated peaks across all timepoints. In fact, the vast majority of the protein-coding gene (PCG) peaks shared across the time-course were upregulated. Gene ontology analysis of these shared upregulated PCG peaks identified enrichment in pathways involved in synaptic plasticity and structural remodeling. In contrast, differential gene expression analysis captured profound transcriptional changes at the acute 1h timepoint involving genes related to synaptic plasticity, which largely dissipated by 24h and 72h. Multiomic integration via Rank-Rank Hypergeometric Overlap (RRHO) profiling identified the most significant concordant overlap between H3K4me3Q5ser enrichment and transcription at the acute 1h timepoint. Taken together, these results demonstrate that ketamine triggers a robustly sustained epigenetic remodeling that outlives its immediate transcriptional wave. We hypothesize that this acts as an "epigenetic priming" mechanism, and future studies will interrogate the functional role of this latent epigenetic state, as well as the requirement of this novel histone mark in establishing and maintaining ketamine's antidepressant efficacy.

Disclosures: Y. Song: None. **G. Di Salvo:** None. **B. Weekley:** None. **I.S. Maze:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.15/M1

Topic: B.05. Synaptic Plasticity

Support: K01MH139990
R01MH116900

Title: Peripheral H3 serotonylation as a mediator of long-term maternal brain remodeling

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Abstract: Pregnancy and the postpartum period drive profound, long-lasting changes in both body and brain, including persistent adaptations in maternal and cognitive behaviors that are mediated, in part, by epigenetic remodeling. We previously demonstrated that histone H3 dopaminylation, a type of covalent modification within the novel class of histone monoaminylation marks, is regulated by reproductive experience. In mouse dams, dopamine fluctuations during postpartum alter hippocampal H3 dopaminylation levels, impacting long-term adaptations in gene expression and behavior. Notably, chronic postpartum stress elevated hippocampal dopamine, leading to disruptions in H3 dopaminylation, gene expression, and corresponding behavioral adaptations. Interestingly, while the periphery undergoes similarly robust physiological remodeling during pregnancy and postpartum, whether these changes contribute to maternal brain reprogramming remains unexplored. This is a critical gap, given recent evidence that circulating factors can modulate hippocampal plasticity. To address this, we performed serum metabolomics across multiple reproductive stages spanning nulliparous, early vs. late pregnancy, early vs. late postpartum, and primiparous states. We identified distinct classes of metabolite dynamics, including a subset that was temporally upregulated across these reproductive stages and remained elevated long after the postpartum period. Strikingly, this class of upregulated metabolites included serotonin. We validated these changes in an independent cohort, and further found that postpartum stress disrupted these serum serotonin elevations. As changes in serotonin can modulate levels of the histone monoaminylation mark, H3 serotonylation, we investigated whether peripheral serotonin changes influence H3 serotonylation of peripheral blood mononuclear cells (PBMCs), the predominant circulating cell population exposed to serum factors. Using CUT&RUN-sequencing, we identified differential H3 serotonylation enrichment in PBMCs that tracked with serum serotonin levels, accompanied by corresponding gene expression changes. Ongoing work will determine the functional

significance of these transcriptional alterations in PBMCs, and whether peripheral serotonin signaling contributes to hippocampal remodeling and maternal behavioral adaptations. Together, these findings suggest a novel body-brain axis through which reproductive experience may epigenetically remodel the maternal brain.

Disclosures: J. Chan: None. **G. Di Salvo:** None. **A. Cunningham:** None. **B. Weekley:** None. **A. Grusca:** None. **I.S. Maze:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.16/M2

Topic: B.05. Synaptic Plasticity

Support: NIMH Grant R01MH116900
Howard Hughes Medical Institute

Title: The estrous cycle regulates histone serotonylation-associated gene expression patterns in the dorsal raphe nucleus

Authors: *R. R. IYER[1], G. DI SALVO[1], B. H. WEEKLEY[1], J. C. CHAN[1], A. M. CUNNINGHAM[1], I. S. MAZE[1,2];
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Abstract: Females are almost twice as likely as males to be affected by Major Depressive Disorder and other mood-related syndromes. One reason for this disparity is that ovarian hormones act as potent neuromodulators and can contribute to mood by affecting the serotonergic system. Indeed, females are at greater risk for mood disorders at times when ovarian hormone levels are changing, and the ovarian hormone estradiol (E2) has been shown to modulate levels of serotonin receptors, serotonin transporters, and proteins involved in serotonin synthesis. However, the impact of ovarian hormones on histone serotonylation (H3K4me3Q5ser), a novel, serotonin-dependent epigenetic mechanism important for neural plasticity and stress responsivity, has not yet been investigated. In the present study, we explored how hormonal status affects histone serotonylation and related gene expression patterns in the dorsal raphe nucleus (DRN) using CUT&RUN sequencing and RNA sequencing. We found that H3K4me3Q5ser enrichment in the DRN changes dynamically across the mouse estrous cycle, with the greatest enrichment being seen during the Proestrus phase (when E2 levels are highest). Furthermore, mice in Proestrus show upregulation of histone serotonylation-marked genes involved in synaptic plasticity and epigenetic regulation. Ongoing and future work will therefore focus on probing the functional implications of these findings on neural signaling throughout the brain, including investigating how histone serotonylation patterns contribute to serotonin-dependent behaviors.

Disclosures: R.R. Iyer: None. **B.H. Weekley:** None. **J.C. Chan:** None. **A.M. Cunningham:** None. **I.S. Maze:** None.

Poster

PSTR084: Transcription and Translation in Plasticity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR084.17/M3

Topic: B.05. Synaptic Plasticity

Support: 1F32MH140478
5R01MH116900

Title: Histone serotonylation recruitment of KMT2E regulates chromatin dynamics in neurodevelopment

Authors: *B. H. WEEKLEY[1], J. CHAN[2], I. S. MAZE[3];
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Abstract: Monoamine neurotransmitters play a key regulatory role during neurodevelopment. In particular, dysregulation of serotonin (5-HT) has been implicated in the pathophysiology of neurodevelopmental disorders, including autism spectrum disorders (ASD), yet the molecular mechanisms underlying 5-HT's contribution to neurodevelopment remains unclear. Our group recently identified covalent monoaminylation of histone H3 (at glutamine 5). Deposition of 5-HT at this site stabilizes neighboring H3K4me3, resulting in the combinatorial H3K4me3Q5ser, recruiting regulatory machinery to increase transcription. During neurodevelopment in mice, we found global shifts in H3K4me3Q5ser enrichment patterns in forebrain, noting alterations in the appearance of broad domains (2.5-35 kb) vs. typical narrow domains (0.5-2.5 kb). Broad H3K4me3 domains have been shown to be enriched at gene loci involved in synaptic signaling in mice and humans, suggesting conservation of neuron-specific function in brain. A screen of known histone "reader" domains identified the plant homeodomain (PHD) finger of *KMT2E* (MLL5) as binding stronger to H3K4me3Q5ser vs. H3K4me3 alone, suggesting it may play a role during neurodevelopment. While MLL5 has been shown to be catalytically inactive, studies highlight its crucial role in neurodevelopment, with mutations in *KMT2E* found in children with symptoms related to ASD, developmental delay, epilepsy, and macrocephaly. To investigate its role in neurodevelopment, we generated *Kmt2e* -/+ & -/- mice. Behavioral assays revealed altered anxiety-like behaviors, deficits in motor coordination, altered sensitivity to sensory stimuli and increased vulnerability to seizures in KO animals. Transcriptomic analysis in P14 animals revealed drastic gene expression changes in cerebellum in KO mice, particularly in genes involved in neurodevelopment and myelination. Electrophysiology recordings revealed significant decreases in cerebellum granule neuron firing and myelination in HET and KO animals, and RNA-seq revealed robust gene expression changes in KO neurons and bulk KO cerebellum. To investigate the mechanism of MLL5 at chromatin, further, we used a FLAG-

tagged *KMT2E* in human cells and performed IP-MS to identify novel binding partners. We discovered that the Nuclear co-receptor (NCoR)/Histone Deacetylase 3 (HDAC 3) complex is strong interactors of MLL5, and that loss of MLL5 in KO mice leads to increased histone acetylation in the P14 cerebellum, driving the gene expression changes. Ongoing experiments seek to use histone acetyltransferase inhibitors to rescue these epigenomic/transcriptomic alterations in HET and KO neurons.

Disclosures: B.H. Weekley: None. **J. Chan:** None. **I.S. Maze:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.01/M4

Topic: B.08. Epilepsy

Title: Employing Multi-Electrode Array (MEA) to Investigate Effects of Anti-Epileptic Drugs on Neuronal Network Activity

Authors: M. FITZPATRICK[1], E. PETTER[1], ***M. FERNANDEZ GARCIA**[2], J. WANG[1], J. M. BROOKS[1];
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Abstract: Epilepsy is a chronic neurological condition characterized by recurrent, unprovoked seizures. Hallmark traits of seizures are neuronal hyperexcitability and hypersynchrony. Multi-electrode arrays (MEA) provide an effective approach to measure neuronal network activity in vitro. In our study, we harnessed the technology to assess effects of anti-epileptic drugs on rodent primary neuronal cultures to model a prophylactic treatment approach to prevent a seizure-like hyperexcitable and hypersynchronous phenotype. Five FDA-approved anti-seizure medications (i.e. stiripentol, phenytoin, rufinamide, carbamazepine, and valproic acid) were tested in this assay. Rat primary cortical neuronal cultures were generated and matured 21-22DIV prior to experiments. All recordings were 10 minutes in duration. The assay was comprised of three phases. First, untreated cultures were recorded to establish baseline neuronal activity. Second, cultures were treated with anti-seizure medications and incubated for 80 minutes with two recordings taken during this period. Finally, hyperexcitability was induced with picrotoxin (PTX) to determine the efficacy of these compounds to suppress an epileptiform-like hyperexcitable phenotype over 60 minutes. Neuronal activity was determined by analyzing changes in mean firing rate. We found that these anti-epileptic drugs reduced picrotoxin-induced hyperexcitability with varying degrees of efficacy, which is also reflected in reported preclinical and clinical data. Stiripentol, carbamazepine, and phenytoin ($n=8$, $p<0.0001$) as well as rufinamide ($n=6$, $p= 0.0002$) significantly suppressed the hyperexcitable phenotype with carbamazepine most closely restoring mean firing rate to baseline activity. Under these conditions, valproic acid ($n=8$, $p= 0.0619$), did not provide a significant reduction in neuronal activity. Using well-established, approved anti-seizure medications, we validated an MEA assay

measuring hyperexcitability of primary neurons and believe that it can be a valuable tool in identifying new anti-epileptic drug candidates.

Disclosures: M. Fitzpatrick: A. Employment/Salary (full or part-time):; Alkermes. **E. Petter:** A. Employment/Salary (full or part-time):; Alkermes. **M. Fernandez Garcia:** A. Employment/Salary (full or part-time):; Alkermes. **J. Wang:** A. Employment/Salary (full or part-time):; Alkermes. **J.M. Brooks:** A. Employment/Salary (full or part-time):; Alkermes.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.02/N1

Topic: B.08. Epilepsy

Support: P3E Research 2025-2026
PROSNI 2024
Enhancing research 2024
Fodecijal/CoecytJal 10229-2022

Title: Hericium erinaceus Extract Reduces Seizure Severity and Epileptiform Activity in a Pilocarpine-Induced Status Epilepticus Model

Authors: *N. J. RAMIREZ RUIZ[1], K. PARDO-PEÑA[2], L. G. MEDINA-CEJA[3];
[1]Dept. of Cell. and Mol. Biol., [2]Dept. of Cell and Mol. Biol., Univ. of Guadalajara, Zapopan, Mexico; [3]Dept. of Cell. and Mol. Biol., Univ. de Guadalajara, Zapopan, Mexico

Abstract: Epilepsyis aneurologicaldisordercharacterizedbyrecurrentseizuresresultingfromabnormalneuronalactivity. Despitetheavailabilityofantiseizuremedications,approximatelyone-thirdofpatientsremaindrug-resistant,highlightingtheneedfornoveltherapeuticapproaches.*Hericium erinaceus* (HE) is amedicinalmushroomwith neuroprotective,antioxidant,andanti-inflammatoryproperties,suggestingitspotentialtoreduceneuronalhyperexcitabilityassociatedwith epilepticseizures.Therefore,this studyevaluatedtheeffectsofHE extractontheseverityofseizurebehaviorandepileptiformactivityinapilocarpine-inducedstatusepilepticus(SE)model.MaleWistarratswereassignedtosix experimentalgroups(n= 3/group):salinesolution(SS), HE 60mg/kg, HE 120mg/kg, pilocarpine(PILO), HE 60mg/kg + PILO,andHE 120mg/kg + PILO. HE extractwasadministeredintragastricallyfor21consecutivedays,including14daysbeforeand7daysafte rSE induction.SE wasinducedbyintracerebroventricularadministrationofPILO (3.3µg). SeizureseveritywasassessedusingtheRacinescale,recordingseizureprogressionandlatencytoSE. Forelectrophysiologicalanalyses,animalswereimplantedwith frontalandparietalsurfaceelectrodesandaguidecannulaintheright lateralventricle.EEGrecordingswereobtainedduringbaseline(days12–13),SE

induction(day14),andpost-SEperiods(days18and21).Epileptiformactivitywasquantifiedbymeasuringdischargeamplitude(μV) andthenumberofepileptiformdischargetrainsthroughouttherecordings.BothHE dosessignificantlyreducedseizureseverity, with only1/3oftreatedanimalsdevelopingmoderateSE. DuringSE theaverageamplitudewas652± 53μV, HEsignificantlyreducedepileptiformactivityreducingtheamplitudeby52.7%(330± 26μV, p=<0.0001,60mg/kg) and37.3%(413± 90μV, p=0.0001,120mg/kg). InThePILO group,thenumberofepileptiformdischargetrainswere112± 12.9with anaveragedurationof31± 3s andtheinterictaltimebetweentrainsof4.8± 1.3s.However, theHE administrationreducedthenumberoftrains(47± 1,p=0.0299),duration(19± 1.4s, p=0.0483)andincreasedtheinterictaltimebetweentrains(130± 12s with 60mg/kg and270± 41s with 120mg/kg, p=0.0178andp=0.0439,respectively).Inthepost-SEperiod,amplituderemainedsignificantlyreducedonday18by47.8%(156± 11μV, p=0.0012,60mg/kg) andonday21by38.0%(176± 17μV, p=0.0010with HE 60and120mg/kg).ThesefindingssuggestthatHE exertsantiseizureeffectsandmayrepresentapromisingcomplementarystrategyforreducingneuronalhyperexcitabilityduringandafterSE.

Disclosures: N.J. Ramirez Ruiz: None. **K. Pardo-Peña:** None. **L.G. Medina-Ceja:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.03/N2

Topic: B.08. Epilepsy

Support: National Institute of Health R01NS120945
National Institute of Health R37N119012
UVA Brain Institute

Title: β-Hydroxybutyrate, A Principal Ketone Body, Regulates Neuronal Excitability Through GIRK Channel Activation

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Abstract: Objective: The ketogenic diet is used to treat drug-resistant epilepsy, yet the molecular mechanisms coupling metabolic state to seizure suppression remain understudied. β-Hydroxybutyrate (β-HB), a principal ketone body, exerts antiseizure effects, yet its downstream ionic mechanisms remain unclear.**Methods**: We used sixty-nine C57BL/6 and microglia-deficient (FIRE) mice, including male and female (4-week-old for *in vitro* and 8-week-old for *ex vivo* experiments). β-HB or saline was administered after the onset of status epilepticus, induced

in mice by continuous hippocampal stimulation. Intrinsic excitability and excitatory synaptic currents on hippocampal granule cells were measured using the patch clamp technique. Calcium imaging was performed after viral delivery of a genetically encoded calcium indicator into the hippocampus. **Results**: In vivo, β-HB rapidly reduced the duration of status epilepticus. At the cellular level, patch-clamp recordings showed that β-HB hyperpolarized dentate granule cells (DGCs), increased action potential threshold, and reduced firing frequency. Moreover, β-HB suppressed excitatory synaptic drives onto downstream CA1 pyramidal cells. At the network-level β-HB perfusion, consistent with the electrophysiological findings, significantly decreased DGC population activity. Mechanistically, pharmacological blockade of G protein-gated inwardly rectifying potassium (GIRK) channels abolishes the β-HB-induced suppression of DGC intrinsic excitability, excitatory synaptic transmission, and population-level activity. In contrast, inhibition of ATP-sensitive potassium (K_{ATP}) channels had no detectable impact on β-HB-mediated modulation of DGC excitability or network responses. **Conclusion**: These findings demonstrate that β-HB modulates neuronal excitability, independent of microglia, underscoring a neuron-intrinsic mechanism. In particular, β-HB modulates neuronal function through GIRK channel activation, providing a mechanistic link between ketogenic states and neuronal excitability and revealing a mechanistic target for ketogenic therapies.

Disclosures: S. Naderi: A. Employment/Salary (full or part-time):; University Of Virginia. **J. Williamson:** A. Employment/Salary (full or part-time):; University Of Virginia. **H. Sun:** A. Employment/Salary (full or part-time):; University Of Virginia. **J. Kapur:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.04/N3

Topic: B.08. Epilepsy

Support: NIH Grant R15NS141197

Title: Optimizing cannabidiol's suppression of hyperexcitability and antiepileptic effects in an ex vivo mouse model of temporal lobe epilepsy

Authors: N. SCHNEIDER[1], S. KENNEDY[1], A. CISNEROS[1], I. CATES[1], J. SWEET[2], E. BUETOW[1], *J. KAPLAN[1];
[1]Psychology Dept., Western Washington Univ., Bellingham, WA; [2]Computer Sci. Dept., Western Washington Univ., Gig Harbor, WA

Abstract: Epilepsy is caused by abnormal electrical activity in neurons that leads to profound changes in brain function. The hippocampus is a common gate of seizure propagation and serves as a therapeutic target to dampen hyperexcitability. Treatment resistance occurs in around 20% of epileptic patients, necessitating the need for improved pharmacological strategies. Cannabidiol (CBD) is a phytocannabinoid that is emerging to treat resistant forms of epilepsy in both children

and adults. We hypothesize that CBD's therapeutic effects occur through an elevation of GABAergic signaling and are enhanced by additional phytochemicals, which together optimally restore the brain's excitatory:inhibitory (E:I) balance. To test this hypothesis, we conducted local field potential recordings from the CA3 hippocampal region in *ex vivo* brain slices obtained from two different mouse genotypes that model non-pathological (C57BL/6J) and pathological (BTBR) seizure susceptibility. We simulated hyperexcitability conditions using a pro-epileptic solution high in K^+ and low in Mg^{2+} which increased the probability of ictogenesis-like activity and elevated spiking frequency. The addition of the $GABA_A$ antagonist, picrotoxin, had a more profound effect on excitability characteristics in C57BL/6J mice compared to BTBRs, which is consistent with a deficiency in GABAergic signaling and indicative of a pronounced E:I imbalance. In both genotypes, CBD delayed the onset of seizure activity and reduced spiking frequency. CBD's ability to dampen hyperexcitability was not blocked by picrotoxin, suggesting that at least some of its therapeutic mechanism against seizure are independent of $GABA_A$ receptor signaling. CBD's therapeutic potential for treating epilepsy and related symptoms is impacted by its wide range of pharmacodynamic targets that are differentially engaged at escalating doses. While this creates a treatment challenge, improved reliability may be achieved through the systematic addition of additional cannabis-derived chemicals such as volatile organic compounds ("terpenes"), which may act on similar or complementary targets to enhance CBD's effects. We have started by adding the prominent terpene, β-caryophyllene, to CBD but found no additional benefit in BTBR mice. Together, our findings confirm CBD's antiepileptic effects but fail to support a $GABA_A$ receptor-dependent mechanism for its action. Upcoming studies will assess the impact of additional terpenes, identify which of CBD's targets are relevant to its antiepileptic effects, and further investigate any genotypic differences between BTBR and C57BL/6J mice.

Disclosures: N. Schneider: None. **S. Kennedy:** None. **A. Cisneros:** None. **I. Cates:** None. **J. Kaplan:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

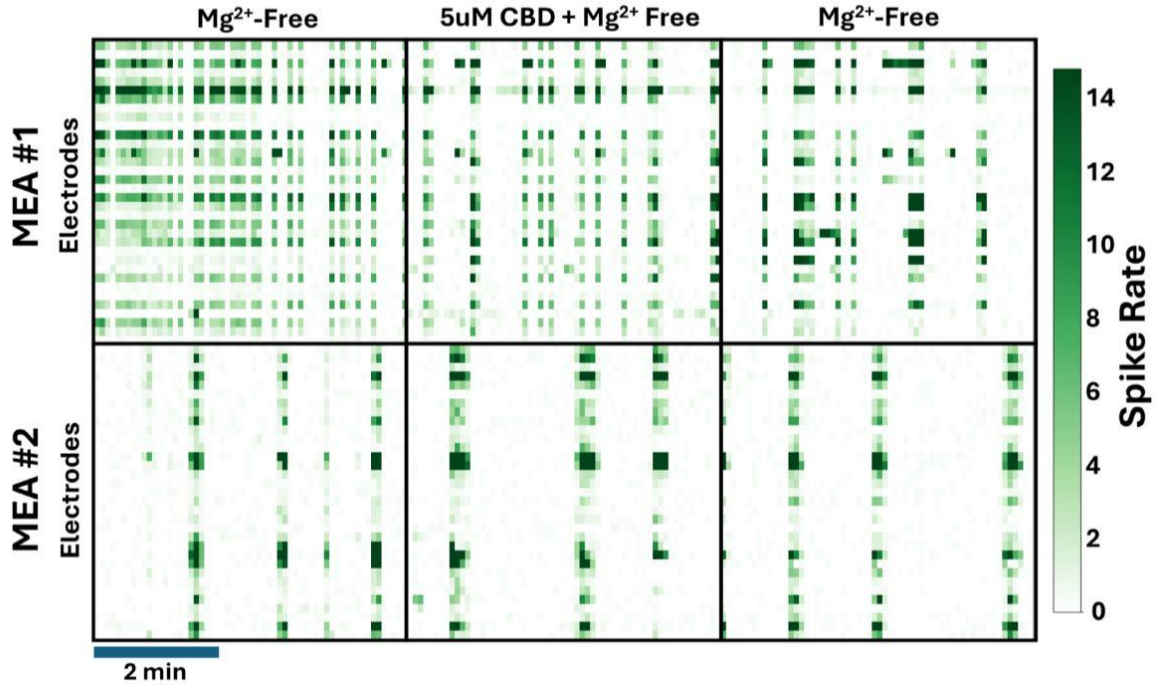
Program #/Poster #: PSTR085.05/Web Only

Topic: B.08. Epilepsy

Title: Acute Cannabidiol Exposure Selectively Restructures Network Activity During Ongoing Mg^{2+}-Free Seizure-Like Activity in Primary Hippocampal Neuronal Cultures

Authors: *K. SHUKOOR[1,2], F. IQBAL[1], U. ZAIDI[1], N. I. SYED[1], K. YUSUF[1];
[1]Cumming Sch. of Med., Univ. of Calgary, Calgary, AB, Canada; [2]Med. Univ. of the Americas, Nevis, Saint Kitts and Nevis

Abstract:



Epilepsy affects over 50 million people worldwide. Despite available treatments, seizures remain inadequately controlled in many patients, emphasizing the need for scalable preclinical platforms to resolve how candidate anti-seizure medications modulate pathological network activity. Cannabidiol (CBD) is approved as an adjunctive therapy for severe pediatric epilepsies, yet its acute network-level effects during ongoing seizure-like activity (SLA) remain incompletely defined. In particular, CBD may affect the pattern of epileptiform firing without reducing global network activity; therefore, both total activity and burst organization were assessed. To test this, we used DIV 18+ primary rat hippocampal neuron cultures on 60-channel microelectrode arrays to determine whether CBD acutely modifies ongoing NMDAR-mediated SLA. SLA was induced using Mg^{2+}-free balanced salt solution, and network activity was compared between cultures receiving 5 µM CBD during ongoing Mg^{2+}-free SLA and vehicle-treated controls. Electrophysiological features were normalized to each MEA's initial Mg^{2+}-free recording window. Spike rate, spike amplitude, interspike interval variability, burst dynamics, and burst-associated spike organization were quantified. Acute 5 µM CBD shifted activity toward more burst-dominated pathological firing patterns. By identifying a selective CBD-dependent shift in burst organization without broad suppression of epileptiform hyperexcitability, these results help characterize the electrophysiological profile of CBD action in mature hippocampal networks and support scalable in vitro MEA assays for mechanism-informed anti-seizure medication screening.

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

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.06/N4

Topic: B.08. Epilepsy

Title: Network Biomarkers of Antiseizure Medication Efficacy Using Routine-Scalp EEG

Authors: *S. PANDIARAJU[1], S. V. SARMA[2];
[1]Johns Hopkins Univ., Ellicott City, MD; [2]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Introduction: Epilepsy affects ~70 million individuals globally, yet anti-seizure medication (ASM) selection remains an empirical trial-and-error process. Clinicians rely on subjective seizure diaries and serum drug levels rather than direct measurements of brain network response. Standard 20-minute routine scalp electroencephalography (rsEEG) relies on visual inspection or static pharmacoEEG features (e.g., bandpower) that collapse time-varying behaviors, failing to capture the dynamic network interactions characterizing the seizure-susceptible brain. This research proposes a precision-medicine framework to address this gap by using rsEEG to measure medication responsiveness.
Methods: We model rsEEG as a linear time-varying system using control-theoretic Dynamic Network Models (DNMs). The state-transition matrix A(t) encodes how activity propagates across channels over time. From A(t), we derive Singular Value Spectral Entropy (SVSE), a network complexity biomarker quantifying whether brain activity is dominated by a few rigid, hypersynchronous modes (low SVSE) or distributed across a richer, more flexible repertoire of functional states (high SVSE). We analyzed a heterogeneous retrospective cohort from Johns Hopkins Hospital consisting of 15 patients with focal epilepsy across four clinical categories: No med (drug-naïve/off-medication), Ineffective (seizures within 6 months), Effective (seizure-free for >=6 months), and Weaned (seizure relapse upon medication withdrawal).
Results: SVSE revealed distinct, quantifiable differences correlated with therapeutic status. The Ineffective group displayed significantly lower SVSE compared to the Effective group ($p=0.01$). This separation supports our hypothesis that ineffective treatment states are characterized by lower complexity and a restricted state-space reflecting underlying epileptogenic potential, while effective treatment shifts networks toward complex neural interactions. The Weaned group exhibited intermediate SVSE values, suggesting a re-emergence of the epileptogenic state. Longitudinal intra-patient analysis demonstrated consistent SVSE states correlating with clinical status, validating its viability for personalized tracking.
Conclusions: SVSE derived from DNMs of rsEEG is a promising, objective biomarker for assessing ASM efficacy. By moving beyond static features, SVSE captures meaningful differences between effective and ineffective therapeutic states, establishing it as a clinically actionable, non-invasive tool to reduce the prolonged trial-and-error process in epilepsy pharmacotherapy.

Disclosures: S. Pandiaraju: None. **S.V. Sarma:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.07/Web Only

Topic: B.08. Epilepsy

Support: CONAHCYT grant CF-2023-I-539
VIEP project 24-0397

Title: Effect of Cannabidiol and Cannabigerol on Nitric Oxide Production in a Pentylenetetrazole-Induced Seizure Model

Authors: *A. PATRICIO-MARTÍNEZ[1], I. LIMON PEREZ DE LEON[1], F. PATRICIO MARTÍNEZ[2];
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Abstract: Epilepsy is a brain disorder characterized by a predisposition to recurrent epileptic seizures resulting from abnormal and synchronous neuronal discharges that trigger excitotoxicity and chronic inflammation in the central nervous system. This condition affects approximately 50 million people worldwide, of whom nearly 30% exhibit drug-resistant epilepsy, highlighting the need for new and effective therapeutic alternatives. The endocannabinoid system has been shown to participate in the regulation of inflammatory processes in seizure models due to its neuromodulatory activity. The aim of this study was to determine the effect of cannabidiol (CBD) and cannabigerol (CBG) administration on seizure activity and nitric oxide production in rats subjected to pentylenetetrazole (PTZ)-induced seizures. Male Wistar rats (250-300 g) were assigned to six experimental groups (Veh/Veh, CBG/Veh, CBG+CBD/Veh, Veh/PTZ, CBG/PTZ, and CBG+CBD/PTZ). CBD (15 mg/kg) and CBG (50 mg/kg) were administered intraperitoneally for seven days prior to seizure induction and 30 minutes before PTZ administration. PTZ (35 mg/kg) was administered every third day for one week. Seizures were video-recorded and classified according to the Racine scale. Cellular extracts from the amygdaloid complex, hippocampus, frontal cortex, and cerebellum were obtained in phosphate-buffered saline (PBS), and stable nitric oxide metabolites (nitrites) were quantified using the Griess assay. The results showed a reduction in seizure severity in the CBG+CBD/PTZ group compared with the Veh/PTZ group. Regarding nitrite levels, treatment with CBG+CBD/PTZ induced changes in nitrite concentrations, particularly in the cerebellum. These findings suggest that CBD and CBG exert a regulatory effect on nitric oxide production and reduce seizure activity in the PTZ model.

Disclosures: A. Patricio-Martínez: None. **I. Limon Perez De Leon:** None. **F. Patricio Martínez:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.08/N5

Topic: B.08. Epilepsy

Support: Key Program of the National Natural Science Foundation of China (32530027)

Title: Single-cell resolved spatial transcriptomic atlas of human TLE-HS uncovers graded neuronal vulnerability and localization immune-glial pathological niches

Authors: ***Y. LIU**[1], Y. HE[1], Y. WEI[1], L. WANG[2];
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Abstract: Hippocampal sclerosis (HS) is a hallmark pathology of drug-resistant temporal lobe epilepsy, characterized by patterned neuronal loss and gliosis, yet its spatial and cellular organization in the human hippocampus remains poorly defined. To resolve ambiguous cytoarchitectural boundaries at the hippocampal margin, we implemented an objective molecular parcellation of the human CA1-Subiculum interface using *FN1* and *ETV1* as definitive transcriptomic boundary markers. Applying this molecularly anchored reference pipeline to single-cell-resolved Stereo-seq datasets of human HS specimens, we identified a pronounced, anatomically graded degeneration of excitatory neurons in CA1, with preferential cell loss in proximal compartments along the proximal-distal axis, accompanied by reduced synaptic integrity and nuclear abnormalities. This neuronal vulnerability is paralleled by coordinated glial remodeling, including widespread expansion of progenitor-like and reactive astrocyte states and focal enrichment of an apoptosis-associated astrocyte state in the fimbria-alveus-stratum oriens system. In this specialized compartment, apoptosis-associated astrocytes spatially co-localize with inflammatory microglia and exhibit enhanced immune- and complement-related interaction signatures, defining a focal immune-glial pathological niche. Beyond CA1, excitatory neurons in CA3-4 display marked transcriptional heterogeneity, including stress-associated states and an *ADCYAP1*-expressing excitatory state enriched for neuropeptide signaling. Although preserved across disease conditions, this state remains embedded within a reactive glial and perivascular microenvironment, suggesting incomplete or context-dependent neuroprotection. Together, our findings reveal HS as a highly structured, spatially organized process involving coordinated remodeling of neuronal states, glial diversity, and immune-glial microenvironments.

Disclosures: Y. liu: None. **Y. He:** None. **Y. wei:** None. **L. Wang:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.09/N6

Topic: B.08. Epilepsy

Support: R01 NS099748

Title: Three-Dimensional Brain Mapping: A Tool for Cognitive Assessment, Brain Function Visualization, and Precision Neurosurgery Planning

Authors: *V. SUN[1], E. ACERBO[2], G. GILMORE[4], A. DICKEY[3], N. G. LAXPATI[5], R. E. GROSS[6], D. L. DRANE[1];
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Abstract: Drug-resistant epilepsy affects approximately 30% of the 1% of the global population with epilepsy. While seizure onset zone localization enables surgical intervention, preserving cognitive functions remains a critical challenge. We aim to construct high-resolution 3D functional maps of the human brain to guide safer resections using a dataset of 104 epilepsy patients. Each patient underwent presurgical evaluation including MRI, CT, and SEEG. Imaging was co-registered and normalized to MNI space, with stimulation contacts clustered at 10 mm^3 resolution and annotated via AAL3. Data were organized into 21 response modalities across six functional domains: (1) language (visual naming, auditory naming, reading, auditory comprehension, semantic processing, speech generation, and repetition); (2) visual (naming, attention, visuoperceptual and spatial processing); (3) auditory (naming, comprehension); (4) affective; (5) cognitive (working memory, mental arithmetic, cognitive slowing, bilingual dissociations); and (6) sensorimotor (sensory processing, motor disruption, déjà vu). We identified reproducible disruption patterns across cortical and subcortical structures. Visual naming clustered in temporal regions such as the fusiform and superior temporal gyri. Language disruptions localized to perisylvian regions including the Rolandic operculum and supramarginal gyrus. Auditory disruptions involved the superior temporal gyrus and Heschl's gyrus. Affective disruptions associated with the temporal pole and parahippocampal gyrus. Cognitive disruptions including mental arithmetic localized to parietal regions such as the angular gyrus and precuneus. This dataset provides the most detailed SEEG-derived 3D functional atlas to date across 21 modalities. These maps improve cognitive risk localization for epilepsy surgery, with ongoing efforts toward modality validation, outcome prediction, and multi-site standardization.

Disclosures: V. Sun: None. **E. Acerbo:** None. **G. Gilmore:** None. **A. Dickey:** None. **N.G. Laxpati:** None. **R.E. Gross:** None. **D.L. Drane:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.10/N7

Topic: B.08. Epilepsy

Support: Fundación IMSS Grant R-2025-785-016
CYTED Grant Red 223RT141

Title: Clinical Characterization and the rs1065852 Polymorphism (CYP2D6) in a Population of Mexican Patients with Controlled and Difficult-to-Control Epilepsy from Three High-Specialty Clinics.

Authors: *I. A. FERIA-ROMERO[1], S. OROZCO-SUAREZ[3], K. BENITEZ RODRIGUEZ[4], D. ORTA[5], M. LEON VAZQUEZ[2];
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Abstract: Introduction. Pharmacological therapy is a standard approach for seizure control in epilepsy; however, approximately 30% of patients do not achieve adequate seizure control despite appropriate medication, irrespective of structural brain damage or identifiable triggers. The influence of non-functional cytochrome variants on pharmacological response remains debated, although the rs1065852 polymorphism (*CYP2D6*) has been identified as a risk factor in the Mexican pediatric population. Objective. The aim of this study is to characterize the clinical features of adult patients with controlled and drug-resistant epilepsy, and to assess differences associated with the presence of the rs1065852 polymorphism in *CYP2D6*. Methods. From May 8, 2025, to May 5, 2026, 82 patients with controlled epilepsy (CTR) and 275 patients with difficult-to-control epilepsy (EFR) were recruited. After one year of follow-up, 64 CTR and 141 EFR patients with complete laboratory data and confirmed adherence to pharmacological treatment were included in the analysis. Blood samples were collected following informed consent approved by the institutional ethics committee. Descriptive statistics, one-way ANOVA, and Chi-square tests were employed to analyze quantitative and qualitative variables. Results. Both groups were similar in median age (33 years), affected lobes (frontal and temporal), absence of laterality predominance, and proportion of structural damage (67% in CTR vs. 79% in EFR). Notable differences included a higher frequency of male sex (24% in CTR vs. 65% in EFR), greater number and diversity of antiseizure medications, and earlier age of disease onset (second decade in CTR vs. first decade in EFR). The rs1065852 polymorphism in *CYP2D6* was present in both groups; however, its presence in EFR patients with structural damage was identified as a risk factor compared to the CTR group (p=0.024), independent of age at seizure onset. Conclusions. The findings demonstrate distinct clinical and pharmacogenetic characteristics among patients with epilepsy recruited from three tertiary care hospitals in Mexico.

Disclosures: I.A. Feria-Romero: None. **S. Orozco-Suarez:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.11/N8

Topic: B.08. Epilepsy

Title: Genotype-phenotype correlations and cell-type-specific somatic mosaicism in pediatric focal cortical malformations

Authors: *A. KO[1], H.-C. KANG[2];
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Abstract: Malformations of cortical development (MCDs) are a major cause of drug-resistant epilepsy in children and are increasingly recognized to result from somatic mosaic variants. While pathogenic variants have been identified in multiple genes, the relationships between genotype, clinical phenotype, and cellular distribution of mosaic variants remain incompletely understood. We analyzed resected brain tissue from 218 pediatric patients with epilepsy-associated MCD who underwent epilepsy surgery. Deep targeted sequencing was performed on resected tissue to identify pathogenic somatic and germline variants. Clinical, neuroimaging, histopathological, and surgical outcome data were compared across genotypes. To investigate the cellular distribution of somatic mosaic variants, fluorescence-activated cell sorting was additionally performed in selected cases using phospho-S6-positive neurons from focal cortical dysplasia (FCD) type II lesions and OLIG2-positive oligodendroglial lineage cells from mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE). Pathogenic variants were identified in 82 of 218 patients (37.6%). Somatic *MTOR* variants were the most frequent finding in FCD type II and hemimegalencephaly, whereas somatic *SLC35A2* variants predominated in MOGHE. Somatic *MTOR* variants were associated with MRI-positive focal epilepsy, localized cortical malformations, and favorable long-term seizure outcomes following surgery. Higher variant allele frequencies correlated with broader cortical involvement and more extensive resections. In contrast, somatic *SLC35A2* variants were associated with infantile epileptic spasms syndrome or Lennox-Gastaut syndrome, lower cognitive function, MRI-negative lesions, and poorer long-term outcomes. Germline *DEPDC5* and *NPRL3* variants were characterized by truncating mutations and very early seizure onset, whereas somatic *AKT3* and *PIK3CA* variants were exclusively associated with hemimegalencephaly. Cell-type-specific enrichment increased detection of low-level mosaic variants and demonstrated preferential localization of pathogenic variants within phospho-S6-positive neuronal populations in FCD and OLIG2-positive oligodendroglial lineage cells in MOGHE. These findings demonstrate distinct genotype-specific clinical and pathological phenotypes across pediatric cortical malformations and reveal lesion-specific cellular distributions of somatic mosaic variants.

Disclosures: A. Ko: None. **H. Kang:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.12/Web Only

Topic: B.08. Epilepsy

Title: Association of the APOE e4 allele and inflammation-related genetic variants in cognitive impairment in patients with drug resistant epilepsy

Authors: *A. LÓPEZ RAMÍREZ[1], C. RODRÍGUEZ-PÉREZ[2], E. ORTIZ[3], V. CAMPOS-PEÑA[4];
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Abstract: Epilepsy is the fourth most common neurological disorder in the world and aboutone-third of adults exhibit drug resistant epilepsy. Temporal lobe epilepsy (TLE) isthe most common form of focal epilepsy, but mesial temporal lobe epilepsy (MTLE)accounts for almost 80% of all temporal lobe seizures. Furthermore, this type ofepilepsy is often accompanied by hippocampal sclerosis (HS). On the other hand,the benign brain tumors can cause epilepsy, called Tumor-related epilepsy (TRE).These tumors are located most commonly in the temporal lobe. Several studiessuggest that there is a positive feedback loop between epileptogenesis and braininflammation. It has also been reported that the apolipoprotein E (APOE) participatesin brain inflammation in epilepsy. In Mexico, there are few studies about geneticvariants involved in neuroinflammation to guide personalized treatment and that cantarget the specific gene variant. For this reason, in this study, some variants presentin *IL1A, IL1B, IL6, IL10, TNF, CRP, PTGS2*, *CR1* and *APOE* genes were evaluatedin 144 Mexican patients with drug resistant MTLE with and without HS, and TRE. Toachieve this study, 16 genetic variants of 9 genes related to neuroinflammation weregenotyped. For this genotyping, as well as APOE, TaqMan probes were used, usingreal-time PCR. The results showed an association with following genotypes: a) G/Gand G/G of the variants rs1800795 (*IL6*) and rs20417 (*PTGS2*), respectively, withTRE. b) The G/G genotype of rs1799724 *(TNF)* with MTLE-HS. c) The genotype C/G(rs1800947) and G/G (rs20417) located in *CRP* and *PTGS2*, respectively, with TLE.Finally, it was observed that the combination of the *ε4 ApoE* allele with the G/G genotype(rs1800795) of *IL6* and G/G (rs20417) of *PTGS2* is associated with TLE. The resultssuggest that these variants could serve as risk biomarkers in the Mexican population.

Disclosures: A. López Ramírez: None. **C. Rodríguez-Pérez:** None. **E. Ortiz:** None. **V. Campos-Peña:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.13/O1

Topic: B.08. Epilepsy

Title: CARDIOVASCULAR RISK BIOMARKERS WITH PREDICTIVE VALUE FOR SUDEP IN PEDIATRIC PATIENTS WITH DRUG-RESISTANT EPILEPSY FROM A TERTIARY CARE HOSPITAL

Authors: *C. GUTIERREZ[1], A. VEGA GARCIA[3], R. PINTO-ALMAZÁN[2], S. OROZCO-SUAREZ[4];
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Abstract: Patients with drug-resistant epilepsy (DRE) are known to have a significantly increased risk of Sudden Unexpected Death in Epilepsy (SUDEP), particularly those with frequent generalized tonic-clonic seizures and poor seizure control. Identifying clinically useful biomarkers in high-risk patients may facilitate early risk stratification and support the implementation of preventive strategies. The aim of this study was to identify cardiovascular risk biomarkers with potential predictive value for SUDEP in pediatric patients with DRE. An exploratory retrospective case-control study was conducted in 48 pediatric patients with epilepsy, including 21 patients with DRE and 27 patients with controlled epilepsy. Demographic and clinical variables, seizure frequency, and the number of antiseizure medications were analyzed. In addition, C-reactive protein (CRP) and intercellular adhesion molecule-1 (ICAM-1) levels were quantified by ELISA, while matrix metalloproteinase-9 (MMP-9) expression was assessed by Western blot. Patients with DRE exhibited a significantly higher seizure frequency and required a greater number of antiseizure medications as compared with the controlled epilepsy group. No statistically significant differences were observed in CRP or ICAM-1 concentrations between groups. However, greater variability in ICAM-1 levels was detected among patients with DRE. Likewise, although MMP-9 expression did not reach statistical significance, an upward trend was observed in the DRE group, which may reflect increased extracellular matrix remodeling and degradation associated with neuroinflammatory processes and ictogenesis. These findings suggest that systemic inflammation and tissue remodeling mechanisms may contribute to the pathophysiology of DRE and support the continued investigation of biomarkers with potential predictive value for SUDEP.

Disclosures: C. Gutierrez: None. **A. Vega garcia:** None. **R. Pinto-Almazán:** None. **S. Orozco-Suarez:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

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Program #/Poster #: PSTR085.14/O2

Topic: B.08. Epilepsy

Support: Institute of Eminence, University of Delhi
MG Grant, University of Delhi

Title: Probiotic-Mediated Modulation of the Gut-Brain Axis Reduces Seizure Burden in Chronic Temporal Lobe Epilepsy

Authors: *R. MITTAL[1], S. SWEETY[2], A. TYAGI[4], J. BANERJEE[5], A. B. DIXIT[3];
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Abstract: Introduction: Temporal lobe epilepsy (TLE) is the most common form of drug-resistant focal epilepsy and is characterized by recurrent seizures, hippocampal neurodegeneration, and synaptic dysfunction. Dysregulation of the Tryptophan-Kynurenine Pathway (TKP) metabolism, leading to alteration in the levels of neuroactive metabolites has been reported in patients with MTLE-HS and is associated with neuronal hyperexcitability and seizure progression. This study investigated whether modulation of the gut microbiota through *Lactobacillus reuteri* supplementation could attenuate seizure severity and influence TKP-associated molecular alterations in chronic TLE. **Methodology:** Male Sprague-Dawley rats received *L. reuteri* (10^9 CFU/rat/day) via oral gavage for 14 days prior to TLE induction. Chronic TLE was established using the Li-Pilocarpine model, and probiotic administration was continued for 28 days following status epilepticus (SE). Seizure severity was assessed using the Racine scale. At study termination, hippocampal, ATL, and neocortical tissues were collected to assess region-specific alterations. H&E and Golgi staining were performed to evaluate neuronal integrity and morphology, while qRT-PCR was used to assess the expression of TKP-related genes and glutamatergic receptor subunits, including NMDA (*NR1, NR2A, NR2B*) and AMPA (*GluR1-4*). **Results:** *L. reuteri* supplementation significantly reduced seizure severity compared with untreated epileptic animals. Histological analyses revealed preservation of neuronal architecture and reduced neurodegeneration in the hippocampus. Golgi staining demonstrated improved dendritic arborization and neuronal morphology. qRT-PCR analysis showed significant region-specific modulation of TKP-associated genes and glutamatergic receptor subunits following probiotic supplementation, with altered expression of key enzymes involved in kynurenine metabolism compared with untreated TLE animals. **Conclusion:** Probiotic supplementation attenuated seizure severity and mitigated neuropathological alterations in chronic TLE. These neuroprotective effects were associated with modulation of the TKP pathway, regulation of glutamatergic receptor expression, and preservation of neuronal structure. These findings highlight the therapeutic potential of microbiota-based interventions in epilepsy and suggest that targeting TKP metabolism may represent a promising strategy for the management of chronic TLE.

Disclosures: R. Mittal: None. **S. Sweety:** None. **A. Tyagi:** None. **J. Banerjee:** None. **A.B. Dixit:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.15/O3

Topic: B.08. Epilepsy

Support: NIH Interagency Agreement Grant AOD26011

Title: Therapeutic Efficacy of Midazolam, Ketamine and Phenobarbital Combination Therapy Against Cholinergic-Induced Status Epilepticus in Female Rats

Authors: *L. KABUI[1], C. R. SCHULTZ[1], H. G. STEIER[1], M. F. STONE[1], T. HUNTER[1], R. MCFARLAND[1], S. CHEN[1], M. DE ARAUJO FURTADO[2], L. A. LUMLEY[1];
[1]U.S. Army Med. Res. Inst. of Chem. Def., Aberdeen Proving Ground, MD; [2]Anatomy, Physiol. and Genet., USU, Bethesda, MD

Abstract: Acute soman exposure irreversibly inhibits acetylcholinesterase and may lead to status epilepticus which when left untreated or treatment is delayed, becomes refractory to treatment with benzodiazepines. Previously, we reported that in adult male rats exposed to soman, the administration of triple anti-seizure medications to include midazolam, ketamine and phenobarbital was more effective in controlling refractory seizure and neurodegeneration compared to midazolam monotherapy. The inclusion of female subjects in preclinical research is increasingly recognized as there maybe sex differences in response to agent exposure and in therapeutic efficacy. To consider potential sex differences in response, we currently report on the efficacy of phenobarbital and ketamine as adjunct to midazolam in adult female rats following soman exposure. Adult female Sprague Dawley rats were implanted with telemetry transmitters for continuous recording of electroencephalographic (EEG) activity. After surgical recovery, rats were exposed to soman and treated with atropine sulfate and the oxime asoxime chloride (HI-6) one minute after exposure. Forty minutes after seizure onset, rats were treated with either midazolam monotherapy, midazolam and ketamine dual therapy or with midazolam, ketamine and phenobarbital triple therapy. Survival as well as seizure data, including spontaneous recurrent seizure, were evaluated. Two weeks after exposure, brains were processed to assess neurodegeneration and neuroinflammation. Triple therapy with phenobarbital, ketamine and midazolam reduced behavioral and EEGraphic seizure, as well as spontaneous recurrent seizures, compared to midazolam monotherapy in soman exposed rats. None of rats treated with triple therapy developed spontaneous recurrent seizure. In addition, rats treated with midazolam also had increased delta band activity, which is associated with neurodegeneration; triple therapy ameliorated this response. Preliminary results suggest that triple therapy attenuated the neuroinflammatory response (Iba1+ staining) and neuronal loss (reduced NeuN+ staining) in female rats exposed to soman compared to those treated with midazolam monotherapy. Dual therapy of either phenobarbital and midazolam or ketamine and midazolam demonstrated improvement over midazolam monotherapy, but was not as effective as triple therapy in these measures. In sum, this study extends previous findings in male rats to female rats, demonstrating

the efficacy of phenobarbital combination therapies that reduce glutamatergic activity, and increase GABAergic activity in treating cholinergic-induced status epilepticus.

Disclosures: L. Kabui: None. **C.R. Schultz:** None. **H.G. Steier:** None. **M.F. Stone:** None. **T. Hunter:** None. **R. McFarland:** None. **S. Chen:** None. **M. de Araujo Furtado:** None. **L.A. Lumley:** None.

Poster

PSTR085: Anticonvulsant and Antiepileptic Therapies

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR085.16/O4

Topic: B.08. Epilepsy

Support: NIH Interagency Agreement Grant AOD26011

Title: Prolonged, Age-Dependent Spatiotemporal Disruptions of Blood-Brain Barrier Integrity Following Cholinergic-Induced Status Epilepticus in Rats

Authors: *T. J. HUNTER[1], J. NIQUET[2], C. R. SCHULTZ[1], M. F. STONE[1], D. A. NGUYEN[1], M. DE ARAUJO FURTADO[3], L. A. LUMLEY[1];
[1]Neurosci., United States Army Med. Res. Inst. of Chem. Def., Aberdeen Proving Ground, MD; [2]UCLA-VAMC, Rancho Mission Viejo, CA; [3]Anatomy, Physiol. and Genet., USU, Bethesda, MD

Abstract: Exposure of rats to organophosphorus nerve agents, such as soman, may lead to benzodiazepine-refractory status epilepticus (SE), which is associated with neurodegeneration, neuroinflammation, and blood-brain barrier (BBB) disruption. Previously, our lab reported age-dependent BBB leakage at 3 days post-exposure (PED3). Adult Sprague Dawley rats (PND70) displayed increased BBB leakage compared to juveniles (PND42). Given that long-term BBB integrity had yet to be investigated, we assessed BBB leakage after 14 days (PED14) and 30 days (PED30) using semi-quantitative analysis of immunoglobulin G (IgG) immunostaining across 5 brain regions associated with SE-induced neuropathology; brain regions assessed included the CA1 of the hippocampus, the medial and lateral thalamus, the piriform cortex, and the amygdala. Juvenile and adult male and female Sprague Dawley rats were exposed to equitoxic dose of soman (0.5 mL/kg SC; 177.6 - 448.8 µg/mL) followed by an admix of 2 mg/kg atropine sulfate and 118.5 mg/kg HI-6 (0.5 mL/kg IM) 1 min after exposure and with 3 mg/kg midazolam (0.5 mL/kg IM) forty minutes after seizure onset; age and sex-matched saline-treated rats served as controls. Following soman exposure and treatment, animals were deeply anesthetized and euthanized via exsanguination at PED14 or PED30 for immunohistochemical analysis of BBB integrity. Juvenile (PND42) rats displayed full restoration of BBB integrity at both PED14 and PED30; however, adult rats (PND70) displayed continued, region-specific BBB disruption at PED14. In adults rats, the most significant BBB disruption occurred in the piriform cortex and lateral thalamus. This disruption expanded to include the medial thalamus at PED30. Taken

together with previous observations at PED3, these data reveal an important, age and region-dependent distinction in BBB recovery following soman-induced SE defined by increased vascular pathology in adults compared to juveniles that may contribute to chronic epileptogenic processes and neuroinflammation.

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Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.01/O5

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

Title: A Biophysically Detailed Human Cortical Model Linking Alzheimer's Pathology to TMS-Evoked Biomarkers

Authors: *T. KHASHAN[1], F. S. BORGES[3], E. URDAPILLETA[4], E. SANTARNECCHI[5], S. DURA-BERNAL[2];
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Abstract: Alzheimer’s disease (AD), the leading cause of dementia, is associated with altered cortical excitability, disrupted excitation-inhibition balance, impaired synchrony, and degraded responses to perturbation. Transcranial magnetic stimulation (TMS) can probe and modulate cortical circuits, with promising results in AD, but mechanisms shaping responses remain unclear and stimulation protocols require personalized optimization. Multiscale biophysical models can integrate data across molecular, cellular and circuit scales to test how AD pathology alters cortical dynamics. We developed a biophysically detailed model of human cortical circuits and TMS stimulation to predict circuit responses to TMS protocols, and evaluate how stage-dependent AD pathology reshapes cortical excitability and TMS-EEG biomarkers. The model, developed in NetPyNE/NEURON, includes IT, PT, and CT pyramidal neurons and PV, SST, and VIP interneurons with active conductances, recurrent excitation-inhibition architecture, short-term plasticity, tonic inhibition, synaptic background, and spatial placement and distance-dependent connectivity based on nano-scale electron microscopy reconstructions of human cortex (H01). Ongoing extensions will add active dendrites, realistic axons and increased cellular diversity to better capture laminar recruitment and stimulation responses. AD-like states are implemented across disease stages using continuous modifiers acting on synaptic, inhibitory, and intrinsic mechanisms, including excitatory and inhibitory synaptic strength, SST-mediated inhibition, tonic and phasic GABA-A signaling, PV fast-spiking function, AMPA/NMDA balance, glutamate-clearance effects, and pyramidal-cell conductances. The model quantifies

membrane responses, spike threshold, firing rate, population recruitment, synchrony, gamma-band power, and LFP/EEG signals, including TMS-evoked potentials (TEPs), during baseline and TMS perturbation. Sensitivity analyses quantify how each AD-related parameter contributes to these outputs, separating synaptic, inhibitory, and intrinsic mechanisms driving altered TMS-evoked activity.We predict a biphasic trajectory where early and intermediate AD-like states result in hyperexcitability through reduced inhibition and altered pyramidal-cell excitability, whereas late-stage states show impaired synaptic propagation, reduced coordination, and degraded evoked responses. Future work includes validation against human TMS-EEG data, AD-relevant EEG signatures, APOE-stratified variants, and optimization of TMS parameters to restore healthier dynamics

Disclosures: T. Khashan: None. **F.S. Borges:** None. **E. Urdapilleta:** None. **E. Santarnecchi:** None. **S. Dura-Bernal:** None.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.02/O6

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

Support: NIH Grant RO1AG068063

Title: Elucidation of hyperarousal in mouse models of Alzheimer's Disease

Authors: *S. J. SLEIMAN[1], K. K. JOYCE[1], A. RAVENS[1], J. S. LORD[1], G. H. DIERING[2]; [2]Cell Biol. and Physiol., [1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Alzheimer’s Disease (AD) is a devastating neurodegenerative disease and leading cause of dementia. Restorative sleep, supported by a healthy circadian rhythm (CR), is essential for brain health and cognitive function. Sleep disruption is a common and early onset feature of AD, apparent well in advance of cognitive decline. Using longitudinal sleep and behavior monitoring, we identified an early-onset, progressive hyperarousal phenotype in mice modeling tauopathy (PS19) and amyloidosis (5xFAD), defined by a marked reduction in sleep and an increase in locomotor activity unique to the dark (active) phase. By crossing 5xFAD with either Tau knock-out (KO) or PS19, we show that sleep disruption in 5xFAD occurs independently of Tau, and that amyloid and Tau pathologies synergize to accelerate progressive sleep loss and exacerbate neuroinflammation. While hyperarousal suggests dysregulation of arousal systems, it remains unclear whether it is driven by alterations in circadian timing, sleep homeostasis, or stress-response pathways. Here, we sought to determine whether hyperarousal in PS19 and 5xFAD mice reflects impaired homeostatic responses to sleep loss and/or circadian dysfunction. In response to increased sleep pressure by acute sleep deprivation (SD), 5xFAD/PS19 mice showed compromised sleep rebound behavior and impaired molecular and physiological responses to SD including cortical induction of Per2, Arc, and Homer1a gene expression, release

of circulating corticosterone, and impaired synaptic glutamatergic plasticity (GRM5 and GluA1 signaling). PS19/5xFAD show robust circadian behavioral rhythms under a constant darkness paradigm. Together our findings suggest that progressive hyperarousal is consistent with dysfunction in homeostatic sleep drive, while CR remains intact.

Disclosures: S.J. Sleiman: None. **K.K. Joyce:** None. **A. Ravens:** None. **J.S. Lord:** None. **G.H. Diering:** None.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.03/O7

Topic:

Support: NIH Grant R01AG078758
NSF GRFP

Title: Time-restricted feeding restores circadian synaptic rhythms and rescues memory in an Alzheimer’s disease mouse model.

Authors: *B. ROUTH[1], L. DOAN[2], J. GOEWEY RUIZ[2], C. R. GIBSON[2], A. R. HYNES[2], L. M. INCE[2], H. A. HOFMANN[3], R. A. MANGIERI[2], L. K. FONKEN[2];
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Abstract: Sleep and circadian disturbances are among the earliest behavioral symptoms of Alzheimer’s disease (AD). Dysregulation of brain circadian rhythms may contribute to neurodegeneration and memory loss; however, direct molecular links between circadian desynchronization, synaptic dysfunction, and cognitive impairment in AD remain poorly defined. AD progression involves converging disruptions in proteostasis, metabolism, inflammation, and synaptic signaling that form a self-reinforcing pathogenic loop, many components of which are normally coordinated across the light/dark cycle. We therefore hypothesized that early AD is characterized by a breakdown in the temporal synchronization of diurnally regulated gene networks that support hippocampal synaptic function. To test this, we adapted weighted gene co-expression network analysis (WGCNA) to identify rhythmic diurnal gene co-expression modules in the mouse hippocampus and examined their disruption in an AD mouse model. This network-based approach revealed an early desynchronization of synapse-enriched co-expression modules by 6 months of age, emerging despite preservation of core circadian clock gene rhythms. We further identified the RNA-binding protein ELAVL4 as a putative upstream regulator of these discordant synaptic gene networks. Disrupted synapse-related transcriptomic rhythms were associated with time-of-day-dependent shifts in excitation-inhibition balance and predicted impairments in hippocampal-dependent memory performance. Finally, implementing a circadian-based time-restricted feeding paradigm in early adulthood

restored ELAVL4-associated co-expression modules and rescued memory deficits. Together, these findings identify behaviorally relevant diurnal hippocampal gene networks that are selectively vulnerable in early AD and demonstrate that a circadian-aligned intervention can restore network synchrony and cognitive function.

Disclosures: B. Routh: None. **L. Doan:** None. **J. Goewey Ruiz:** None. **C.R. Gibson:** None. **A.R. Hynes:** None. **L.M. Ince:** None. **H.A. Hofmann:** None. **R.A. Mangieri:** None. **L.K. Fonken:** None.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.04/O8

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

Support: 5R01NS121300-05

Title: A peptidergic interneuron-microglia axis drives synaptic loss and cognitive decline in Alzheimer’s disease

Authors: *C. DAMIAN[1], P. DONG[1], W. T. FARMER[1], D. MELVILLE[1], B. ASRICAN[1], D. S. TART[2], L. G. COLEMAN, Jr.[1], J. SONG[1];
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Abstract: Microglial activation and neural circuit dysfunction are hallmarks of Alzheimer’s disease (AD), yet the neural circuit signals that govern microglial state transitions in vulnerable brain regions remain poorly understood. Here, we identify hilar cholecystokinin-expressing interneurons (CCK-INs) in the dentate gyrus as a region-specific regulator of microglial state via activity-dependent CCK peptidergic signaling. In both human and mouse AD tissues, hilar CCK-INs exhibit dystrophic pathology accompanied by reduced local CCK levels that coincide with microglial activation and memory impairment. Selective CCK loss induces microglia-enriched AD risk genes and recapitulates inflammatory, synaptic, circuit, and behavioral deficits associated with AD. Restoring CCK tone in AD brains reprograms microglia, preserves excitatory synapses, and rescues cognition in a microglia-dependent manner. Notably, early PKM2-dependent metabolic reprogramming precedes CCK-IN dysfunction, and correcting this restores interneuron activity and prevents downstream pathology. Together, these findings define a causal, interneuron-microglia signaling axis linking circuit dysfunction to neuroinflammation and identify therapeutic entry points at the circuit-neuroimmune interface.

Disclosures: C. Damian: None. **P. Dong:** None. **W.T. Farmer:** None. **D. Melville:** None. **B. Asrican:** None. **D.S. Tart:** None. **L.G. Coleman:** None. **J. Song:** None.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.05/P1

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

Support: Canadian Institutes of Health Research (CIHR PJT191806)
NIH R01AG084681

Title: Linking cognitive resilience related changes in human cortical microcircuits to EEG biomarkers across the AD disease progression in silico.

Authors: *K. CHEN[1], J. S. HE[2], F. MOGHBEL[3], H. YAO[4], A. T. GUET-MCCREIGHT[5], E. HAY[6], B. STEFANOVIC[7];
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Abstract: The concept of cognitive resilience to Alzheimer’s disease (AD) has emerged from observations that some individuals maintain better-than-expected cognitive performance despite substantial AD neuropathology. Recent human studies revealed that AD resilience is associated with distinct neurophysiological changes in specific inhibitory neuron subtypes and synaptic proteins compared to cognitively impaired AD patients. However, how these resilience-related changes influence brain circuit dynamics and manifest in clinically relevant EEG features remains poorly understood. This knowledge gap limits the early identification of individuals without high resilience potential and the development of early interventions to delay or prevent dementia. As mechanistic investigation of human brain circuits in vivo is limited, we employed a detailed computational model of human cortical microcircuit to reveal EEG biomarkers of AD-susceptibility and AD-resilience-related changes. We first modeled healthy human canonical cortical microcircuits to reproduce experimentally observed baseline activity and responses to a 1-minute, 3 Hz sensory stimulation. We then incorporated AD-susceptibility and AD-resilience-related changes as a continuous pseudotrajectory across the AD progression. Our preliminary results demonstrate that simulated spiking and EEG signals show distinguishable AD-susceptibility versus AD-resilience contrast beginning in the asymptomatic stage of AD, primarily through separation in baseline periodic components and stimulus-evoked changes in aperiodic activity. This project aims to provide a mechanistic framework linking cellular pathology to circuit dynamics and EEG biomarkers, so as to help guide earlier identification of individuals at different levels of risk for AD-pathology induced cognitive decline.

Disclosures: K. Chen: None. **J.S. He:** None. **F. Moghbel:** None. **H. Yao:** None. **A.T. Guet-Mccreight:** None. **E. Hay:** None. **B. Stefanovic:** None.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.06/P2

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

Title: Longitudinal EEG reveals progressive network dysfunction in the ARTE10 mouse model of Alzheimer's disease

Authors: M. VILLALBA[1], C. ALLIOUX[2], B. CARABALLO[1], C. DUMONT[1], E. GRONLIER[1], ***C. ROUCARD**[2], Y. ROCHE[2], D. OLSEN[4], J. VOLLE[3], C. HABERMACHER[1];
[1]R&D, [2]SynapCell, Saint-Ismier, France; [3]R&D, SynapCell, Saint Ismier, France; [4]Taconic, Åbyhøj, Denmark

Abstract: Alzheimer's disease (AD) is characterized by a prolonged preclinical phase during which progressive brain dysfunction precedes overt cognitive decline. Identifying translational functional biomarkers and preclinical models that reliably capture early network alterations remains critical to improve disease characterization and therapeutic development. Electroencephalography (EEG), a highly translational technique, offers a unique opportunity to investigate disease-related brain dysfunction in patients and preclinical models. The ARTE10 transgenic mouse model co-expresses mutant human amyloid precursor protein (APP) and presenilin-1 (PS1) and develops early, robust amyloid pathology. Despite its behavioral characterization, its neurophysiological phenotype remains poorly defined. Here, we performed longitudinal EEG and sleep phenotyping of ARTE10 mice and WT littermates to characterize spontaneous cortical activity, sleep-wake architecture, and auditory evoked responses. Twenty-four-hour polysomnographic EEG recordings were conducted at 5 and 12 months, corresponding to early amyloid deposition and advanced disease, respectively. Auditory steady-state responses (ASSRs) and auditory event-related potentials (AERPs) were recorded longitudinally at 5, 7, 9, and 12 months to probe cortical synchronization and sensory processing. ARTE10 mice exhibited age-dependent alterations in sleep-wake organization, with increased nocturnal wakefulness, reduced Non-Rapid Eye Movement (NREM) sleep, and altered REM dynamics, resembling disturbances reported in AD patients. EEG spectral analysis revealed an early-onset phenotype at 5 months characterized by cortical hyperexcitability, increased high-frequency activity, and epileptiform discharges. With aging, this phenotype progressively evolved toward cortical slowing and pronounced reduction in interhemispheric functional connectivity, reflecting large-scale network disorganization. Auditory paradigms uncovered early and persistent impairments in cortical processing, including reduced 40-Hz ASSR power and synchronization, atypical AERP waveforms, and impaired sensory gating. These abnormalities preceded overt cognitive impairment. Together, these findings demonstrate that ARTE10 mice exhibit early, persistent, and progressive EEG abnormalities aligned with electrophysiological signatures of human AD. Longitudinal EEG, sleep-wake metrics, and auditory evoked measures provide robust translational biomarkers, supporting the ARTE10 model for investigating AD from prodromal to symptomatic stages and for evaluating therapeutic strategies.

Disclosures: M. Villalba: 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. **E. Gronlier:** A. Employment/Salary (full or part-time):; SynapCell. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell. **D. Olsen:** A. Employment/Salary (full or part-time):; Taconic. **J. Volle:** A. Employment/Salary (full or part-time):; SynapCell. **C. Habermacher:** A. Employment/Salary (full or part-time):; SynapCell.

Poster

PSTR086: Alzheimer's Disease: Neural Circuit Disruption I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR086.07/P3

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

Support: NIH Grant R01AG069227
Mary Gates Endowment for Students

Title: Texture-Dependent Sensorimotor Patterns Under Scopolamine and Nerve Block

Authors: *H. RYU[1], S. PUNACHA[2], L. FAVOUR[3], J.-S. LI[1], D. TANG[3], F. I. ARCE-MCSHANE[4];
[1]Dept. of Oral Hlth. Sci., [2]Univ. of Washington, Seattle, WA; [3]Univ. of Washington, Seattle, WA, ; [4]Univ. of Washington, Univ. of Washington, Seattle, WA

Abstract: Oral health issues have been associated with age-related dementias such as Alzheimer’s disease (AD), a neurodegenerative disease affecting tens of millions of individuals worldwide. Clinically, AD is characterized by behavioral and cognitive decline. Changes in brain connectivity with aging and AD are also linked to motor impairments such as dysphagia (difficulty swallowing), which is prevalent in moderate to severe AD. Oral texture perception relies on coordinated activity across cortical circuits, yet how these representations are altered under cognitive and sensory impairment remains unclear. We aim to investigate how cortical representation of texture in brain regions changes under memory impairment alone and in combination with reduced sensory input. In our study, we quantified neural coherence during active texture discrimination using coherence values derived from Utah Arrays across three cortical regions (M1, S1, PF). Data were collected from one healthy non-human primate (N = 1). The subject performed a texture discrimination task by licking a textured plate while receiving flavored juice as a reward. Each trial lasted 5 seconds, during which the subject licked one of two texture plates varying in coarseness. Administration of scopolamine, an M1 muscarinic receptor antagonist, was used to model the cognitive impairments observed in AD. Local nerve block was administered to reduce peripheral tactile sensation at the tongue. Coherence values were compared across three conditions (control, scopolamine, and scopolamine + nerve block) for two texture plates (#1: smooth, #2: rough). For each texture plate, intercortical region pairs

(M1-S1, S1-PF, M1-PF) were evaluated using Kruskal-Wallis tests, followed by post-hoc pairwise comparisons when significant. Exploratory two-way ANOVAs were also conducted to examine interactions between condition and texture.

Disclosures: H. Ryu: None. **S. Punacha:** None. **F.I. Arce-McShane:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.01/P4

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

Title: Correlating Transcriptomic Signatures with Protein Biomarkers to Evaluate Mechanism-Specific Drug Responses in Alzheimer's Disease iPSC Neurons

Authors: *Y. ANZABI, A. SAADIN, C. KETTULA;
Ricoh Biosci., Baltimore, MD

Abstract: Drug development in Alzheimer's disease is suffering from the high failure rate, which is frequently attributed to poor genetic diversity in preclinical models, such that the complex transcriptomic landscape of human therapeutic targets has not been fully captured. We established a panel of iPSC-derived excitatory neurons derived from 10 sporadic AD patients and 5 healthy donors, and maintained them in 2D monocultures for six weeks. Over the duration of the culture, the effects of the following 2 compounds on the levels of Aβ42 secretion and pTau accumulation were evaluated by ELISA: Memantine HCl (NMDA antagonist), and ABT-089 (α4β2 nAChR partial agonist).Additionally, the transcriptome of untreated excitatory neurons in this panel were examined by bulk RNA-sequencing to identify differences in biological pathways associated with the disease by Gene Set Enrichment Analysis (GSEA) and Normalized Enrichment Score (NES). Glutamatergic and calcium signalling pathways were strongly upregulated in 9/10 AD donors (L-glutamate import NES +2.13; cytosolic calcium NES +2.77). Despite this, memantine produced attenuated and variable ELISA responses across donors, and responder status could not be predicted by pathway enrichment alone. This likely reflects compensatory transcription masking functional receptor loss at the protein level, decoupling gene expression from drug sensitivity.For ABT-089, cholinergic pathway enrichment was modest across the panel, yet ERK1/2 signalling was markedly elevated in AD neurons (NES +2.78; 8/10 donors). Stratification by Aβ42/40 ELISA response identified a responder subgroup characterised by significantly higher baseline NF-κB enrichment compared to non-responders (difference in NES values +3.6, p=0.001). Responder status was therefore predicted by pre-treatment effector pathway activation rather than target receptor expression.These findings demonstrate that baseline transcriptomic signatures can evaluate drug responses at the individual donor level. Downstream effector state, not receptor pathway enrichment, is the primary determinant of drug sensitivity. This patient-derived panel represents a genetically diverse and

translationally relevant platform for preclinical AD drug evaluation and for prospectively identifying patient subpopulations likely to benefit from specific therapeutics.

Disclosures: Y. Anzabi: None. **A. Saadin:** None. **C. Kettula:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.02/P5

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

Support: Boettcher Foundation
BrightFocus Foundation
Colorado State University College of Veterinary Medicine and Biomedical Sciences

Title: Chlorogenic acid reverses amyloid beta-induced hippocampal hyperexcitability by modulating the fast-inactivating transient A-type potassium current

Authors: *S. SHAH[1], M. TORRES[3], R. LEE[2], S. KIM[2];
[2]Biomed. Sci., [1]Colorado State Univ., Fort Collins, CO; [3]Univ. Federal Fluminens, Niterói, Brazil

Abstract: Alzheimer’s disease (AD) is the most common form of dementia. However, there is no known cause or cure for AD. Therefore, understanding the neural mechanisms of AD pathogenesis is of the utmost importance for better diagnostic and therapeutic development. Both preclinical and clinical studies have shown that cortical and hippocampal hyperactivity is found in the early stages of AD. In patients, hyperexcitability is strongly linked to cognitive decline. Hyperactivity in the brain is thought to be a driver of AD pathology and cognitive impairment. Importantly, beta-amyloid peptide (Aβ) is a major trigger of neuronal hyperexcitability. Therefore, targeting to reverse Aβ-induced hyperexcitation in neurons can be a novel therapeutic strategy. Chlorogenic acid (CGA) is a major compound in coffee, often reported to offer neuroprotective benefits. However, the direct mechanisms are unknown. Previous works, including ours, have shown that CGA treatment significantly reduces neuronal activity. Therefore, we hypothesize that CGA reverses Aβ-induced neuronal hyperexcitation. To test this idea, we use live Ca^{2+} imaging in cultured mouse hippocampal neurons to directly measure neuronal activity. As shown previously, Aβ treatment is sufficient to induce neuronal overactivity. CGA treatment reverses the Aβ-induced toxic effects in hippocampal neurons. Additionally, CGA enhances voltage-gated potassium (K+) channel activities, specifically modulating the fast-inactivating transient A-type K+ current. In fact, we discover that the CGA effects on Aβ-induced neuronal hyperexcitation are abolished by blocking K+ A-type currents. Our findings thus suggest that CGA can prevent neuronal hyperexcitation via modulating K+ A-type currents, which offers neuroprotective benefits in AD.

Disclosures: S. Shah: None. **M. Torres:** None. **R. Lee:** None. **S. Kim:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.03/P6

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

Support: U19 AG066567

Title: Direct exposure to dementia-associated anticholinergics induces Alzheimer's disease-related neuronal pathologies in hiPSC-derived cortical neurons

Authors: *I. K. A. PRANOTO[1], K. HUI[2], T. SCHWARZE-TAUFIQ[2], S. GRAY[3], J. E. YOUNG[2];
[2]Lab. Med. and Pathology, [1]Univ. of Washington, Seattle, WA; [3]Pharm., Univ. of Washington, SEATTLE, WA, WA

Abstract: Anticholinergic medications (ACMs) are widely prescribed for managing various conditions, including depression, allergies, and an overactive bladder. Despite their efficacy, pharmacoepidemiology studies have long reported increased dementia risk associated with prolonged use of certain ACM classes. However, a key limitation of these findings is the difficulty in distinguishing whether the increased dementia risk is linked to the underlying health condition being treated, or to the drug's activity itself, referred to as confounding by indication bias. Finally, the mechanisms by which ACMs perturb neuronal function contributing to Alzheimer's disease (AD) pathogenesis remain unclear. To address this, we use human-induced pluripotent stem cell-derived neurons (hiPSC-Ns) to directly examine the effects of various ACM classes on molecular processes implicated in AD.
We generated 12 hiPSC-Ns from donors in the Adult Changes in Thought (ACT) study in Seattle, WA. We treated hiPSC-Ns with drugs in the dementia-linked ACMs classes (antidepressants & bladder antimuscarinics) and those with no dementia association (antihistamines & antispasmodics). In these neurons, we evaluated their effects on molecular hallmarks of AD by measuring the levels of neurotoxicity, tau phosphorylation, and secreted amyloid-beta peptides, along with assessing neuronal synaptic activity.
Only exposure to dementia-linked ACMs, but not others, elevates neurotoxicity. Interestingly, while dementia-linked ACMs do not meaningfully alter tau phosphorylation in hiPSC-Ns, we detected a marked increase in the ratio of secreted $A\beta^{1-42}$ / $A\beta^{1-40}$ peptides, suggesting a pathogenic shift in amyloid processing. We also observed that dementia-linked-ACMs significantly reduced neuronal firing activity, an effect that is reversible upon drug removal, indicating active perturbation of neuronal synaptic function. Our study demonstrates that dementia-linked ACMs directly disrupt neuronal processes implicated in AD. We provide a molecular basis for ACMs-linked dementia described in longitudinal studies, establishing them as a potential modifiable risk factor for AD. These mechanistic insights will enable more precise

anticipation of the long-term effects of prolonged ACM exposure and lay the groundwork for preemptive prescribing strategies that could meaningfully reduce dementia risk in vulnerable cohorts.

Disclosures: I.K.A. Pranoto: None. **K. Hui:** None. **T. Schwarze-Taufiq:** None. **S. Gray:** None. **J.E. Young:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.04/Q1

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

Support: NIH Grant R16NS134541

Title: Intersection of Sleep, Stress, and β-Amyloid Accumulation in C. elegans

Authors: *M. BARSEGYAN[1], C. VAN BUSKIRK[2];
[1]Dept. of Biol., California State University, Northridge (CSUN), Northridge, CA; [2]Biol., Cal Sate Univ. Northridge, Northridge, CA

Abstract: Alzheimer's disease (AD) is associated with progressive accumulation of β-amyloid (Aβ) plaques. While metabolic stress promotes Aβ aggregation, it remains unclear whether Aβ reciprocally modulates stress responses. We used *Caenorhabditis elegans* strains expressing the human $A\beta_{1\text{-}42}$ peptide, a model system for Aβ aggregation, to investigate whether Aβ alters stress resistance. Stress resistance was first assayed by survival following exposure to ultraviolet (UV) light. We found that Aβ expression in neurons, but not in muscle, increases post-UV survival, pointing to a hormetic effect. The tissue specificity of this effect is consistent with the known systemic coordination of *C. elegans* stress responses by the nervous system. Stress resistance was also assayed via stress-induced sleep (SIS), which is triggered by exposure to damaging conditions. Given our finding above, we predicted neuronal Aβ expression would reduce SIS. Contrary to this prediction, Aβ in both tissues enhanced rather than reduced SIS, revealing a novel interaction between Aβ and sleep regulation. To tease apart the interactions of Aβ with sleep and stress, Aβ-expressing transgenes were examined in a genetic background in which sleep-promoting neurons can be activated independently of cellular stress. In this context, we found sleep to be enhanced by Aβ expression in either neurons or muscle, confirming a specific interaction between Aβ and sleep, and placing this impact downstream of sleep neuron activation. We are currently investigating how sleep in turn impacts Aβ aggregation.Together, our findings highlight a novel interplay between Alzheimer's disease-associated protein aggregation and sleep-regulating pathways that warrants further investigation.

Disclosures: M. Barsegyan: None. **C. Van Buskirk:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.05/Q2

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

Title: Amyloid-beta impairs long-term potentiation and promotes calcium-dependent cytotoxicity through alpha7 nicotinic acetylcholine receptors

Authors: I. G. PEREZ[1], O. E. IMIRUAYE[1], M. A. RAMIREZ[3], D. S. HAN[2], S. BHATTACHARYA[2], ***K. D. PARFITT**[3];
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Abstract: Alzheimer's disease (AD) is marked by neuronal loss and impaired synaptic plasticity due to amyloid-beta (Aβ) accumulation. Aβ has previously been shown to have high affinity for the alpha7 nicotinic acetylcholine receptor (α7nAChR); however, how this interaction contributes to Aβ-induced cell death and hippocampal dysfunction remains poorly understood. We examined whether Aβ(1-42) increases calcium-dependent cytotoxicity through α7nAChR signaling, and whether Aβ exposure impaired long-term potentiation (LTP). IMR32 cells were exposed to Aβ (1-42) for 24 hours, and viability was measured using SYTOX green live-cell imaging. In separate experiments, cells were pretreated for 30 minutes with either an intracellular calcium chelator BAPTA-AM (2 uM) or the α7nAChR antagonist methyllycaconitine (MLA; 2 nM) before Aβ exposure. Using an intracellular calcium chelator, BAPTA-AM, improved cell viability from 39 % to 85 % with BAPTA-AM in cells exposed to Aβ (two-way repeated measures ANOVA, $p < 0.001$). MLA also improved cell viability when exposed to Aβ, increasing mean viability from 45% to 85 % (two-way ANOVA, $p < 0.001$). To determine whether Aβετα was also associated with synaptic dysfunction, field excitatory postsynaptic potentials (fEPSP) were recorded from CA1 stratum radiatum while stimulating the CA3 Shaffer collateral pathway in hippocampal slices prepared from 3 - 7-month-old 5XFAD or age-matched litter-mate control C57Bl/6 mice. LTP magnitude was quantified during the 50-60-minute window following two theta-burst stimulations. Aβετα-incubated slices and slices from 5xFAD mice showed reduced LTP compared to control slices (Aβ vs control, 112.5 ± 7.7% vs 150.6 ± 4.3% of baseline, N=5 and 6 slices, $p=0.0182$; 5xFAD vs control, 117.8 ± 9.7% vs 150.6 ± 4.3% of baseline, N= 6 slices, $p=0.0380$; one-way ANOVA with Tukey's post hoc test). MLA-treated Aβ slices showed no significant change in LTP magnitude compared to Aβ alone (117.8 ± 5.5% vs 112.5 ± 7.7%). Basal synaptic transmission (input-output relationships) was also assessed and showed reduced slopes in 5xFAD and Aβ-treated slices compared to WT slices, while short-term plasticity (paired-pulse facilitation (PPF)) was not affected by the Aβ status. These data show that Aβ promotes calcium-dependent cytotoxicity through α7nAChRs and impairs hippocampal synaptic plasticity, as shown in AD-relevant mouse models.

Disclosures: I.G. Perez: 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.; Wells Fargo

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Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.06/Q3

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

Support: NRF Grant RS-2022-NR070151
NRF Grant RS-2024-00419358

Title: Behavioral Analysis of Cognitive Impairment in a Rat Model of Noise-Induced Hearing Loss and Amyloid-β Pathology

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Abstract: Hearing loss has been increasingly recognized as a modifiable risk factor for cognitive decline and Alzheimer’s disease (AD). However, how auditory dysfunction interacts with amyloid-β (Aβ)-related pathology to influence distinct cognitive domains remains incompletely understood. In the present study, we used a Wistar rat model combining repeated noise exposure with continuous Aβ infusion to examine behavioral alterations associated with auditory impairment and AD-related pathology. Animals were assigned to four experimental groups according to noise exposure and infusion condition: non-noise ACSF, non-noise Aβ, noise ACSF, and noise Aβ. Baseline auditory function was confirmed using auditory brainstem response (ABR) before experimental manipulation. Aβ or artificial cerebrospinal fluid was continuously infused for two weeks using an osmotic pump. Cognitive performance was evaluated using the Y-maze spontaneous alternation task and the Barnes maze task, allowing assessment of working memory, spatial learning, and spatial memory-related behaviors. Y-maze analysis showed that the noise Aβ group tended to exhibit reduced spontaneous alternation

performance compared with the non-noise ACSF group, suggesting a potential impairment in working memory performance when noise exposure and Aβ pathology coexist. Barnes maze performance was analyzed using conventional quantitative parameters, including distance moved, total latency, and number of errors. In addition, search strategy analysis was performed to further characterize spatial exploration patterns. For this purpose, Barnes maze Unbiased Strategy Classification (BUNS), a machine learning-based tool developed for automated classification of rodent search behavior in the Barnes maze, was applied together with a modified manual classification system based on previous literature. This study explores working and spatial memory-related behavioral changes in an animal model combining noise-induced auditory impairment and Aβ-related pathology, and is expected to provide fundamental insights into the interaction between auditory dysfunction and AD-related pathology.

Disclosures: J. Park: None. **Y. Park:** None. **J. Yang:** None. **A.A. Kahinga:** None. **S. Hwang:** None. **M. Chang:** None. **J. Sung:** None. **M. Park:** None. **S. Jun:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.07/Q4

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

Support: NIA grant U54AG054345

Title: A1527G variant of ABCA7 drives cortical astrocyte loss and amyloid deposition in a LOAD mouse model

Authors: *C. BERNABE[1,2], K. P. KOTREDES[3], R. PANDEY[3], G. W. CARTER[3], M. SASNER[3], A. OBLAK[2], G. R. HOWELL[3], B. T. LAMB[2], P. R. TERRITO[1,2];
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Abstract: Multiple genome-wide association studies (GWAS) have identified ABCA7, a member of the ABC1 lipid transporter subfamily, as a risk gene for Alzheimer's disease (AD). In the brain, ABCA7 is expressed across various cell types, including neurons, astrocytes, microglia, endothelial cells, and pericytes, and variants in this gene have been associated with disrupted lipid handling, impaired phagocytosis, and amyloid accumulation. Despite this, the mechanisms by which ABCA7 variants translate to AD risk remain poorly understood. The IU/JAX/PITT MODEL-AD Center identified the *A1527G* variant in *ABCA7* (*ABCA7*A1527G*) as a putative LOAD risk factor. CRISPR/CAS9 was first used to introduce *Abca7*A1527G* variant to B6.*APOE4.Trem2*R47H* (LOAD1) mice to assess the transcriptional profiling on brain hemispheres from different ages. The *Abca7*A1527G* was then incorporated into B6.*APOE4.Trem2*R47H*.hAb (LOAD2) mice to further evaluate its contribution to LOAD. Female and male LOAD2.*Abca7*A1527G* and LOAD2 mice were characterized at 4, 12, and 24

months using the following phenotyping pipeline: behavior, PET/CT, multi-omics, fluid biomarkers, neuropathology, and targeted protein analysis. While no aging cognitive deficit was observed in LOAD2.*Abca7*A1527G*, PET/CT imaging revealed significant sex- and region-dependent increases in brain glycolysis, accompanied by reduced tissue perfusion, which was accompanied by marked reductions of vasculature-supporting astrocytes in cortical regions. This resulted in a progressive age-related uncoupled phenotypes between 4-12 and 4-24 months. These changes were further supported by brain transcriptional profiling showing *Abca7*A1527G*-associated alterations in granulocyte/neutrophil migration, and insulin receptor signaling. Supporting this uncoupled profile, peripheral inflammation diverged from central, where plasma IL6, IL10, and TNFα were elevated in *A1527G* carriers, while brain IL4, IL12, TNFα, and CXCL1 were reduced, and brain IL2 and IL10 were elevated regardless of age. Interestingly, 24-month-old ABCA7 cohorts had elevated soluble and insoluble Aβ40 and Aβ42 in both plasma and brain samples, which we further confirmed by discrete ThioS-positive amyloid accumulation primarily in cortical regions. Data collected to date support a model in which variations in *ABCA7* confer AD risk through interactions between cerebrovasculature, glia, Aβ deposition, and peripheral immune cells.

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Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.08/Q5

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

Title: Tyrosine-Kinase/PYK2 dependent suppression of homomeric Kv1.1 and Kv1.2, and heteromeric Kv1.1/1.2 channels: Implications for Alzheimer’s Disease

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Abstract: The roles of Aβ in the pathogenesis of Alzheimer ’s disease (AD) includes disruption of synaptic function and plasticitymechanisms thought to underlie learning and memory. How these abnormal processes arise is incompletely understood.Evidence suggests dysregulation of intracellular Ca2+ is involved in alterations of neuronal excitability and neurodegeneration in AD. We have focused on the involvement of voltage-gated potassium channels in these processes, particularly Kv1.x channels as they regulate Ca2+ influx and inhibition may lead to hyperexcitability and neuronal death. We previously observed rapid, robust Aβ(1-42)-suppression (~50% in 30 min) of macroscopic homomeric Kv1.1, Kv1.2, and heteromeric Kv1.1/1.2 channel currents. Broad spectrum PTK inhibition bygenistein eliminated Aβ(1-42)-

suppression indicating a role forPTKs in Aβ-suppression. We asked whether PTK PYK2, which suppresses Kv1.2: 1) suppresses Kv1.1 and Kv1.1/1.2 channels,2) which amino acid residue(s) mediated PYK2-suppression, and 3) the extent that Aβ(1-42)-suppression involved PYK2. In-vitro transcription reactions were utilized to generate PYK2, Kv1.1 and 1.2 cRNA. Kv1.2 Y132F mutants generated through site-directed mutagenesis. Stage V/VI X. laevis oocytes were injected with ~1ng of cRNA respectively. Effects of bathapplication of 1μM of Aβ(1-42) and 100nM PMA were evaluated using TEVC electrophysiology. Recordings obtained 24hrs post injections. Co-expression of PYK2 (gifted by Dr. Johannes Hell) witheither WT Kv1.2, Kv.1.1, or heteromeric Kv1.1/1.2, and PYK2 activation by PMA, produced significantly greater currentsuppressions (~80%, n's=10, 4, 4), compared to suppression produced by PMA-alone (~50%; p's < 0.05, 0.02, 0.01) Mutant homomeric Kv1.2 Y132F channels exhibited reducedsuppression by Aβ(1-42) than WT Kv.1.2 (17%, n=10 vs. 48%, n=10; p < 0.0004). The additional suppression by PYK2 involved Y132, as suppression of the mutant Kv1.2-Y132F by PMA+PYK2 (58%, n=8) was significantly less than WT Kv1.2 and no different from suppression of either WT or Y132F Kv1.2 by PMA alone. Combined activated PYK2 + Aβ(1-42) produced no greater suppression of Kv1.2 currents than activated PYK2 (79%, n=4 vs 82%, n=4,) suggesting PYK2 activation occluded Aβ(1-42)-suppression. PYK2 activation suppresses Kv1.1, Kv1.2 and heteromeric Kv1.1/1.2 channels, as does Aβ(1-42). PYK2-activation by Aβ(1-42) appears to play a major role in Aβ(1-42)-suppression of Kv1.2 through Y-phosphorylation of Y132. Suppression of Kv1.2, 1.1 and 1.1/1.2 channels by PYK2 may causeexcitotoxicity via excess Ca2+ influx and glutamate release, contributing to AD pathogenesis.

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Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.09/Q6

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

Support: RF1AG061846
5R01AG075862
5R01AG077046
T32 AA007456
R01 AG073418
U01 AG088679
R01 AG056259
R35 AG071734

Title: Extracellular-Vesicle Transfer from Alzheimer's Disease Organoids to Healthy Tissue as a Potential Non-Cell-Autonomous Mechanism of Amyloid-β Spread

Authors: *S. CHITTAL[1], A. BALISTRERI[1], N. TURNER[1], S. LABRA[1], J. R. YATES, III[1], S. A. LIPTON[2], J. W. KELLY[3];
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Abstract: Alzheimer's disease (AD) affects over 55 million people worldwide and is the leading cause of dementia. One contributing factor is the progressive accumulation of amyloid-β (Aβ) pathology, but the mechanisms driving this spread remain poorly understood. Extracellular vesicles (EVs) play a critical role in cell-to-cell communication in all eukaryotic organisms and have been proposed as a potential mechanism for non-cell-autonomous propagation of pathological cargo from neuron to neuron. Using human iPSC-derived cerebrocortical organoids carrying the familial AD mutation PSEN1 M146V and an isogenic wild-type (WT) control, we isolated EVs from conditioned media to characterize their cargo. Western blot and ELISA confirmed that Aβ42 is present within tetraspanin-positive EV isolates from both genotypes. Additionally, proteomic profiling revealed that AD organoid EVs are enriched in secretory autophagy regulators RAB8A/B, suggesting increased autophagic secretion activity, which could cause cells to secrete autophagy cargo into the extracellular space rather than degrade it. Thus, to test whether AD organoid-derived EVs directly transfer amyloid pathology to healthy tissue, AD organoids were labeled with a conjugated oligoelectrolyte endosomal membrane probe and co-cultured with WT organoids for seven days. Live-cell imaging revealed probe-labeled puncta within WT organoids, consistent with direct endosomal membrane transfer. Following tissue clearing and Aβ immunostaining, WT organoids co-cultured with AD organoids showed significantly increased Aβ signal compared to WT-WT co-cultures ($p = 0.0134$), suggesting the presence of EV-mediated amyloid seeding from AD EVs to healthy tissue. These findings show that Aβ peptides can transfer from AD to WT cerebrocortical organoids, at least in part via EVs, resulting in a significant increase in amyloid burden in healthy tissue. The endosomal origin of this transfer and altered secretion machinery suggests EV secretion is a possible mechanism of non-cell-autonomous Aβ spread in human brain tissue.

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Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.10/R1

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

Support: NIH Grant HL140182
NIH Grant HL66299
NIH Grant HL148069

Title: The relationship between amyloid precursor protein and ExoY

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Abstract: Amyloid precursor protein (APP), the parent molecule for amyloid beta (Aβ), has been identified as antimicrobial within the brain and has been shown to retain its properties in the lungs. Pulmonary microvascular endothelial cells (PMVEC) predominately express longer isoforms of APP (APP770) and tau compared to their cerebral counterparts. Recent studies have shown that ICU patients with ventilator-associated pneumonia have elevated levels of tau and Aβ in their bronchoalveolar lavage fluid, plasma, and cerebrospinal fluid, correlating with chronic memory impairments.
Pseudomonas aeruginosa, a bacterium that causes pneumonia, especially in ICU patients, utilizes a type III secretion system to inject bacterial exoenzymes, including ExoY, into host cells. When injected into a host mammalian cell, ExoY becomes active and functions as a promiscuous cyclase, upregulating the production of both purine (cAMP and cGMP) and pyrimidine (cUMP and cCMP) cyclic nucleotide monophosphates. The elevation in cNMPs leads to the activation of protein kinases A and G, which phosphorylate tau, leading to its dissociation from microtubules and subsequent tau aggregation. The supernatants taken from PMVECs infected with the *P. aeruginosa* $ExoY^+$-strain caused neuronal tau aggregation in HEK293 cells expressing human 2N4R tau isoform, as measured by bimolecular fluorescence complementation, indicating cytotoxic tau presence. Brain tissue homogenates from wild type mice, but not tau knockout mice, infected with $ExoY^+$ in the lung replicated these findings. While the pathway for tau's response to pulmonary infections and its impact on the brain tissue is established, the APP-and-Aβ response mechanism remains unclear.Our studies demonstrate that tau expression in PMVECs influences both the APP fragmentation and the $Aβ_{40}$ production during an $ExoY^+$ infection. Western blot analysis of supernatant samples from wild type PMVECs revealed infection-induced APP cleavage, which was significantly reduced in tau knockout cells. Cell lysate western blots also showed distinct APP banding patterns based on the presence or absence of tau. In addition, MSD assays indicated lower $Aβ_{40}$ levels in tau-knockout compared to tau-expressing cells following infection. Bulk RNAseq and Western blot analyses revealed no change in APP transcript and protein expression between wild type and tau knockout cells, although a shift toward non-amyloidogenic pathways was suggested in the absence of tau. Taken together, these results indicate that tau modulates APP response during host-pathogen interaction in lung endothelial cells.

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Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.11/R2

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

Title: Noise-Induced Hearing Loss Exacerbates Pathological Oligomeric Amyloid-Beta and Impairs Cognition

Authors: *M. CALVANO[1], J. YAO[2], K. M. BIESZCZAD[3];
[1]Rutgers Univ., Englewood Cliffs, NJ; [2]Otolaryngology, [3]Psychology, Behavioral and Systems Neurosci., Rutgers Univ., Piscataway, NJ

Abstract: Hearing loss is the #1 modifiable risk factor in middle-aged adults for Alzheimer's disease (AD) and related dementias (ADRD). Loud noise exposure induces one of the most common forms of hearing leading to permanent noise-induced hearing loss (NIHL). Although mounting epidemiological evidence suggests a strong association between hearing loss, age-related cognitive decline, and AD/ADRD, a mechanistic link between hearing loss and AD pathology remains unclear. A key limitation in the field is the inability to experimentally isolate the onset and potential causal influence of sensory loss on neurodegenerative disease progression. By targeting NIHL, we provide a translationally relevant and temporally controlled inducible animal model of hearing loss to investigate the temporally dynamic interactions of NIHL on AD pathology and subsequent effects on cognitive dysfunction. First we establish a gerbil model to study the interaction between NIHL and AD pathology by either inducing permanent NIHL (loud noise exposure: 120 dB SPL for 2 hrs) or **injecting human amyloid-beta (**Aβ) oligomers intracerebroventricularly into separate groups of young adult gerbils. Histology for AD hallmarks (e.g., Aβ, phospho-tau) will be compared in hippocampus, auditory cortex (AC), and parietal cortex (PC) **between** four groups: (1) NIHL alone, (2) Aβ alone, (3) Aβ + NIHL, and (4) controls. We then identify neuroinflammatory markers and epigenetic modifications that may **explain how NIHL induces persistent and progressive effects in disease**. **Our preliminary data show that** Aβ alone and NIHL alone induce AD-like pathology in gerbil **AC, PC and hippocampus. We will next determine the cognitive consequences of NIHL and** Aβ interactions by **assessing decision-making task performance. In this task, animals are required to categorize and distinguish slow versus fast presentation rates of visual cues. Behavioral performance will be correlated with AD-related pathological markers across brain regions. Together, this work will define how acquired hearing loss interacts with amyloid-beta pathology to accelerate neurodegenerative changes and impair cognitive function.**

Disclosures: M. Calvano: None. **J. Yao:** None. **K.M. Bieszczad:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.12/R3

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

Title: Post-Translational Modifications Differentially Modulate Amyloid-β Aggregation and Microglial Inflammatory Responses in Alzheimer's disease

Authors: *P. KANIK[1], S. GUPTA[2];
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Abstract: Amyloid-β42 (Aβ42) is an intrinsically disordered peptide whose aggregation and accumulation in the brain are hallmark pathological features of Alzheimer's disease (AD), promoting microglial activation and neuroinflammatory responses. Post-translational modifications (PTMs) of Aβ are increasingly recognized as important regulators of its aggregation, toxicity, and pathogenicity. In particular, phosphorylation and acetylation alter the peptide's charge distribution thereby modulating its aggregation propensity. We explored the effects of phosphorylation and acetylation on the aggregation propensity and structural characteristics of Aβ-derived model peptides. Furthermore, we examined the impact of phosphorylated Aβ peptide on microglial activation and neuroinflammatory responses using the human microglial cell line. We synthesized and characterized site-specific Aβ model peptides (wild-type and modified) using Fmoc-based solid-phase peptide synthesis (SPPS) and mass spectroscopy. Peptide aggregation behavior was evaluated using Thioflavin-T (ThT) fluorescence assays, sedimentation analysis, and microscopic techniques. To assess the neuroinflammatory effects of PTM-dependent aggregation, monomeric and aggregated Aβ model peptides were tested in human microglial cells. Cellular responses were evaluated by measuring ROS production, cell viability, cytokine levels and inflammatory marker expression. ThT assay findings indicated that site-specific phosphorylation and acetylation altered the aggregation profiles of Aβ model peptides, with phosphorylated and dual-modified peptides exhibiting fluorescence patterns distinct from those of the unmodified peptide. In microglial cells, phosphorylation-dependent effects were observed on oxidative stress and inflammatory responses. Phosphorylated Aβ was associated with reduced ROS production in the aggregated state, while comparatively smaller effects were observed for monomeric species. ELISA-based cytokine profiling indicated that phosphorylation of Aβ was associated with reduced secretion of pro-inflammatory cytokines compared with the unmodified peptide. Consistent with these findings, ICC analysis revealed that aggregated unmodified Aβ induced elevated IL-6 and IL-1β expression, whereas phosphorylated Aβ exhibited reduced pro-inflammatory marker expression and altered TGF-β1 signalling. Collectively, these findings highlight the importance of Aβ post-translational modifications in shaping aggregation-associated neuroinflammatory responses and provide a foundation for future studies aimed at targeting pathogenic Aβ species in AD.

Disclosures: P. Kanik: None. **S. Gupta:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.13/R4

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

Support: NIH Grant R35NS116852

Title: Amyloid beta mechanistically linked to clinical GABAergic dysfunction in Alzheimer's disease: amyloid beta aggregate accumulation exacerbates neuronal extracellular chloride dysregulation

Authors: *K. P. NORMOYLE, K. J. STALEY;
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Abstract: Dysfunctional GABAergic circuitry underlies key hallmarks of Alzheimer's disease (AD), such as amnestic episodes and executive impairments. Chloride (Cl) homeostasis is in turn central to GABAergic function, as the $GABA_A$ receptor canonically conducts Cl anions inward along a Cl concentration gradient. Maintenance of this gradient provides an inward driving force for Cl conductance and is central to GABAergic inhibition. We recently discovered that alterations in the immobile polyanions of the extracellular matrix (ECM) can alter extracellular chloride concentration ($[Cl^-]_o$) and demonstrated that removal of immobile ECM anions caused increased $[Cl^-]_o$. Widely recognized AD initiating factor amyloid beta (Aβ) is densely anionic and collects in the extracellular space (ECS), but the mechanism by which is leads to AD remains unclear. We hypothesized that deposition of anionic Aβ displaces $[Cl^-]_o$, consistent with hyperexcitability observed proximal to Aβ plaques in animal models, representing a potential mechanistic link between Aβ accumulation and AD clinical symptoms through GABAergic circuitry disruption. We used 2-photon Fluorescence Lifetime Imaging (FLIM) of a custom chloride-sensitive fluorophore constrained to the ECS by conjugation with 10KDa dextran (ABP-dextran) to quantify $[Cl^-]_o$ non-invasively. *In vivo* observations in 9 or 19mo APP/PS1 mice are through implanted cortical windows. Acute brain injury is modeled using 2-photon photolysis of single neurons in organotypic cultures of hippocampal slices expressing intraneuronal chloride ratiometric reporter Super Chlomeleon (SClm). Aβ aggregate accumulations were identified with 2-photon compatible CRANAD-3. We previously demonstrated that neuronal $[Cl^-]_o$ is only about half that of bulk CSF Cl both *in vitro* and *in vivo*, and that $[Cl^-]_o$ is anticorrelated with immobile extracellular anions in brain. Here we demonstrate that $[Cl^-]_o$ is significantly reduced in proximity to Aβ accumulations, just as more ice in a glass analogously leaves less room for liquid. Our data are consistent with rodent model observations of hyperexcitability in proximity to Aβ plaques as well as clinical data linking dysfunctional GABAergic circuits with amnestic episodes and cognitive impairment. Displacement of $[Cl^-]_o$ by Donnan displacement forces is an underappreciated mechanism through which Aβ aggregate accumulation may directly impact GABAergic signaling, driving $[Cl^-]_o$ to pathologically low levels and undermining effective conductance of Cl with immediate implications for the treatment of AD in addition to AD associated epilepsy and potentially other neurodegenerative disorders.

Disclosures: K.P. Normoyle: None. **K.J. Staley:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.14/R5

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

Title: SIRT7 inhibition lowers $A\beta_{42}$ levels in APP Swe/Ind transfected SH-SY5Y cells

Authors: *K. SHARMA, M. M. MIGLIORE;
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Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disease, pathologically characterized by increasing burden of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein. SIRT7 is a NAD^+ dependent deacetylase, mainly localized in nucleolus. Previous studies have shown the role of SIRT7 in regulation of cellular processes such as oxidative stress and apoptosis, which are involved in AD pathology raising the possibility that it may influence amyloid precursor protein processing and Aβ production. As the role of SIRT7 in AD pathology remains unclear, the aim of this study is to investigate the effect of its inhibition on $A\beta_{42}$ secretion in an *in vitro* model of AD. SH-SY5Y cells were transfected using a plasmid containing APP Swe/Ind mutation to induce $A\beta_{42}$ production. YZL-51N, a known and selective inhibitor of SIRT7 with IC_{50} of 12.7 μM, was administered in 5 μM, 10 μM, 15 μM, 20 μM, 25 μM and 30 μM concentrations. Media was collected after 24 and 48 hrs of treatment, and extracellular $A\beta_{42}$ levels were quantified using ELISA. Transfection with APP Swe/Ind showed significant increase in extracellular $A\beta_{42}$ secretion as compared to control cells. Treatment with YZL-51N showed dose-dependent decrease in $A\beta_{42}$ levels at both 24- and 48-hours time points. Following a two-way ANOVA analysis, a statistically significant decrease was observed in both time and dose parameters, with the highest effect, a 58.5 % decrease, observed at the 30 μM dose after 48 hours of treatment. These findings show that SIRT7 inhibition attenuates $A\beta_{42}$ production in transfected SH-SY5Y cells, highlighting the potential of SIRT7 inhibition as a possible therapeutic target for AD.

Disclosures: K. Sharma: None. **M.M. Migliore:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.15/R6

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

Support: R01 AG084646

Title: Non-Enzymatic Regulation of BACE1 by alpha/beta-hydrolase domain containing 6 (ABHD6) in a model of Alzheimer's Disease

Authors: *M. EKANE[1], J. YIN[1], S. SONG[2], G. LI[1], S. ZHAO[1];
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Abstract: The enzyme α/β-Hydrolase Domain-Containing 6 (ABHD6), which hydrolyzes monoacylglycerol (MAG) lipids such as the endocannabinoid 2-arachidonoylglycerol (2-AG), plays a key role in neurotransmission, inflammation, and brain energy metabolism. Research has shown that inhibition of ABHD6 is protective against the development of inflammation-related disorders and microglial proliferation. Emerging evidence suggests that inhibition of ABHD6 also plays a role in neurodegenerative diseases such as Alzheimer's disease (AD), but its role in AD pathophysiology remains unclear. In this study, we investigated the role of ABHD6 in modulating AD pathology. To test this, we generated a global ABHD6 knockout 5xFAD mouse model and an amyloid precursor protein (APP)-overexpressing neuroblastoma cell line (SH-SY5Y) and evaluated APP processing and neuropathological outcomes. Brain tissue was analyzed for neuroinflammation, microgliosis, and Aβ deposition. Neuroblastoma cells were treated with siRNA or an adenoviral vector to knock down or overexpress ABHD6, respectively. Our results show that ABHD6 deletion in 5xFAD mice significantly reduced amyloid plaque burden in the brain. Notably, ABHD6 knockdown in vitro reduced BACE1 and APP C-terminal fragments while increasing full-length APP expression, suggesting a mechanistic link to APP processing and Aβ production. These findings reveal that ABHD6 contributes to AD pathology by promoting Aβ accumulation, possibly through the modulation of BACE1. Our data position ABHD6 inhibition as a modifier of AD pathology and underscore its broader relevance beyond endocannabinoid signaling in the brain.

Disclosures: M. Ekane: None. **J. Yin:** None. **S. Song:** None. **G. Li:** None. **S. Zhao:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.16/Web Only

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

Support: This work was supported by the Section of Postgraduate Studis and Research, Academic Secretary of National Polytechnic Institute, Mexico.

Title: Amyloid beta effects on brain glutamate dehydrogenase activity as a new neurotoxicity mechanism and possible early indicator of Alzheimer's disease

Authors: *L. A. VEGA RASGADO;
BIOQUIMICA, ESCUELA NACIONAL DE CIENCIAS BIOLOGICAS, I.P.N., CDMX, Mexico

Abstract: Alzheimer's disease (AD) is the most prevalent dementia worldwide, characterized by the presence of amyloid-beta (Aβ) plaques, which unfortunately can only be detected post-mortem to confirm the diagnosis. Understanding metabolic alterations caused by Aβ and their relation to the severity of AD and their expression is critical for developing effective treatments. Glutamate (Glu) is the most abundant and principal excitatory neurotransmitter in the central

nervous system, participating in functions such as learning and memory, therefore could be fundamental in the progression of AD. The enzyme glutamate dehydrogenase (GDH, EC 1.4.1.3) reversibly catalyzes the oxidative deamination of Glu, releasing α-ketoglutaric acid (α-Kg), ammonia, and NAD(P)H. Therefore, GDH has the dual capacity to fix the ammonium ion, which levels must be strictly regulated due to its toxicity, and to act as an energy source in brain oxidative metabolism. Therefore, the *"in vitro"* effects of Aβ on mouse brain GDH activity were investigated by analyzing both directions of the reaction, using a spectrophotometric method based on the Strecker method. The results indicate that Aβ increases the oxidative deamination of Glu, while inhibiting the reductive amination of α-Kg. These effects are dependent on the concentration and treatment time. This would result in a decrease in Glu levels, protecting neurons against death due to excitotoxicity. Simultaneously, the generation of α-Kg would be promoted, supplementing energy in response to the decrease in brain metabolism. This would produce oxidative stress, thus it could be one of the mechanisms by which Aβ causes such effect. Since described changes on GDH activity are observed at very short treatment times and low concentrations, they are considered as Aβ effects previously to extra neuronal plaques formation. It is concluded that Aβ modifies brain GDH activity shifting reaction equilibrium to Glu oxidative deamination, an effect that precedes the formation of amyloid plaques. Therefore, changes in GDH activity could represent a potential early indicator of Alzheimer's disease, which would allow for much more timely treatment that would considerably reduce cognitive decline.

Disclosures: L.A. Vega rasgado: None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.17/S1

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

Support: NIH T32 Grant 2T32GM133364-06

Title: Characterization of Neuronal Primary Cilia in an Amyloid-Beta Based Alzheimer's Model

Authors: *K. S. BALASUBRAMANIAN[1], S. S. KHAN[2];
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Abstract: Alzheimer's disease (AD) represents one of the most prevalent neurodegenerative diseases for which only mildly effective treatments currently exist. One defining feature of AD is the accumulation of amyloid beta (Aβ) plaques, but recently dysfunction of neuronal primary cilia has also been implicated in AD pathogenesis. The primary cilium (PC) is a microtubule-based organelle emanating from the neuronal cell surface that senses environmental cues and transduces key intracellular signaling pathways for neuronal homeostasis. Importantly, neuronal PC are dynamic, changing in length or receptor composition in response to pathological or

physiological stimuli. Mouse models of AD demonstrate altered PC structure and composition in hippocampal neurons. However, these changes have not been mapped to neuron subtypes that are uniquely vulnerable to AD pathology, such as hippocampal neurons. To address this gap, we utilized an immunohistochemical approach to analyze hippocampal neuron primary cilia structural changes in 5xFAD mice that harbor three mutations in the amyloid precursor protein (APP) and two mutations in presenilin 1 (PSEN1) and exhibit significant Aβ pathology. In 5xFAD mice, hippocampal neurons exhibit ciliary shortening at 6 months, a timepoint when amyloid pathology is already present and AD-associated learning and memory deficits emerge. These findings complement our *in vitro* work, as amyloid precursor protein (APP) overexpression leads to shorter primary cilia in human retinal pigment epithelium (RPE) cells. Taken together, these results suggest that APP overexpression can cause structural changes in hippocampal neuronal primary cilia and RPEs, possibly through a conserved mechanism. To further determine disease relevance, our future work will address the unique vulnerability of hippocampal neurons to primary cilia dysfunction and the functional consequences of this phenotype in 5xFAD mice.

Disclosures: K.S. Balasubramanian: None. **S.S. Khan:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.18/S2

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

Title: Longitudinal Characterization of Sleep and EEG in the ARTE10 Mouse Model

Authors: A. BERNARDO[1], L. STAM[1], L. DLUGOSZ[1], S. THEVARKUNNEL[1], L. GRIFFIN[2], M. JACOBSON[2], S. STERLACE[2], ***D. M. HUTCHESON**[1], J. HUXTER[3];
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[3]Transpharmation Ltd, Sandwich, Kent, United Kingdom

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, amyloid-β (Aβ) pathology, and a range of neuropsychiatric and sleep-related disturbances. The ARTE10 transgenic mouse model, which co-expresses human APP and PS1 mutations associated with familial AD, develops early and robust cerebral Aβ deposition, providing a valuable platform for translational AD research.In the present study, we performed a longitudinal characterization of ARTE10 mice to evaluate the development of electrophysiological, and sleep-related phenotypes across disease progression. N=32, n=16 male WT and 16 male homozygous ARTE10 mice were surgically prepared for use with the non-tethered TaiNi EEG system. All mice underwent monthly assessments from 5 to 15 months of age using quantitative electroencephalography (qEEG) and sleep architecture analysis. Electrophysiological recordings revealed a pronounced hyperexcitability phenotype in ARTE10 mice. Compared with wild-type controls, transgenic animals exhibited significant alterations in

sleep architecture, including reduced non-rapid eye movement (NREM) sleep at later ages. qEEG analyses demonstrated persistently elevated spectral power across multiple frequency bands, including increased theta-band activity. Furthermore, ARTE10 mice displayed a marked reduction in normal sleep spindle activity and an increased incidence of spike-and-wave discharges (SWDs), predominantly during wakefulness, indicative of aberrant network excitability and seizure-like activity.Collectively, these findings demonstrate that the ARTE10 mouse develops robust and progressive phenotypes that recapitulate key pathological and neurophysiological features observed in AD patients, including sleep disruption and cortical hyperexcitability. The model exhibits sustained survival to 15 months of age while providing an early and measurable disease phenotype, supporting its utility for evaluating both disease-modifying and symptomatic therapeutic interventions targeting AD and its associated comorbidities.

Disclosures: A. Bernardo: A. Employment/Salary (full or part-time):; Transpharmation. **L. Stam:** A. Employment/Salary (full or part-time):; Transpharmation. **L. Dlugosz:** A. Employment/Salary (full or part-time):; Transpharmation. **S. Thevarkunnel:** A. Employment/Salary (full or part-time):; Transpharmation. **L. Griffin:** A. Employment/Salary (full or part-time):; Taconic. **M. Jacobson:** A. Employment/Salary (full or part-time):; Taconic. **S. Sterlace:** A. Employment/Salary (full or part-time):; Taconic. **D.M. Hutcheson:** A. Employment/Salary (full or part-time):; Transpharmation. **J. Huxter:** A. Employment/Salary (full or part-time):; Transpharmation.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.19/S3

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

Title: Distinct Neurodegenerative Disease-Associated Biotypes Revealed By Blood Biomarkers

Authors: *J. MENDIOLA[1], E. N. WILSON, Jr.[2];
[1]Neurosci., Brown Univ., PROVIDENCE, RI; [2]Neurosci., Brown Univ., Providence, RI

Abstract: Blood biomarkers have revolutionized diagnosis, prognosis, and treatment monitoring in neurodegenerative diseases (NDs). Neuroimaging biomarker modalities, including MRI and PET, often capture clinical ND biotypes that follow predictable neuropathological trajectories. However, whether blood biomarkers show similar patterns is unknown. A predictable, measurable, sequence of blood biomarker changes would offer significantly improve personalized disease staging for prognosis while also providing a sensitive framework by which to monitor treatment response. 688 participants spanning the Alzheimer’s disease (AD) continuum from cognitively unimpaired (CU), MCI to AD (mean age 71.02 +/- 8.3 years) were drawn from the Stanford ADRC and the Stanford Aging and Memory Study (SAMS). Plasma biomarkers included P-Tau181, P-Tau217, Aβ42, Aβ40, GFAP, and NfL. Blood biomarker

biotypes were determined using the pattern of binary blood biomarker abnormality. Individual biomarker cutoffs were optimized to maximize sensitivity and specificity in distinguishing CU from AD. Cognition was assessed using the Montreal Cognitive Assessment (MoCA). Mixed effects models compared clinical data and cognitive trajectories across identified biotypes. A sequential ordering of blood biomarker changes emerged such that blood biomarker abnormality proceeded from blood biomarker negativity to amyloid abnormality alone, followed by subsequent abnormality in GFAP, P-Tau181/P-Tau217, and then NfL. Two additional biotypes were observed: GFAP abnormal only and Aβ+, GFAP-, P-Tau+ - a biotype seemingly sparing GFAP. Remarkably, greater than 90% of study participants from across the AD continuum fit neatly into one of these blood biomarker biotypes. Advancement through these biotypes was associated with poorer cognition and predicted worse cognitive trajectories. ND blood biomarker biotypes show a stereotyped progression of blood biomarker changes across the AD continuum. Adopting this framework is likely to enhance diagnostic and prognostic accuracy and treatment monitoring in ND.

Disclosures: J. Mendiola: None. **E.N. Wilson:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.20/S4

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

Title: Investigating glucocorticoid-mediated protection against acute amyloid-beta cytotoxicity in SH-SY5Y cells

Authors: O. BOTWINICK, *M. VASEFI;
Univ. of Houston, Houston, TX

Abstract: Amyloid-beta (Aβ) oligomer accumulation is a primary driver of neurodegenerative pathology in Alzheimer's disease. While chronic elevated cortisol is classically associated with exacerbated neuronal injury, acute stress-response dynamics may paradoxically trigger transient protective signaling pathways. This study investigated the early, potentially non-genomic protective capacity of acute glucocorticoid modulation against acute Aβ1-42 oligomer-induced cytotoxicity. SH-SY5Y neuroblastoma cells were cultured in DMEM with 10% fetal bovine serum and treated for 24 hours in serum-free medium with pre-aggregated Aβ1-42 oligomers at concentrations ranging from 1 to 10 μM. $A\beta_{1-42}$ oligomerization was verified using dot blot analysis, MALDI-TOF, and Thioflavin-T fluorescence, and cytotoxicity was measured using the MTT assay. To assess the effect of acute cortisol pretreatment on Aβ-induced cytotoxicity, cells were pretreated with cortisol prior to Aβ exposure. Statistical analysis was performed using one-way ANOVA with Tukey’s post-test. Aβ1-42 application produced a robust, dose-dependent decrease in cell survival. Strikingly, acute 10-minute cortisol pretreatment significantly rescued cell viability across all tested Aβ insult concentrations, while showing no baseline cytotoxicity

when administered alone. Although cortisol itself is not proposed as a therapeutic agent, these findings support further investigation of stress response mechanisms that may reveal new targets for neuroprotection in Alzheimer's disease.

Disclosures: O. Botwinick: None. **M. Vasefi:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.21/S5

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

Title: In vivo imaging to test the effects of anti-amyloid immunotherapy on vascular amyloid

Authors: *G. SHAUTIDZE[1], P. PIKUS[2], H. CHEHADE[1], H.-Y. CHU[1], G. W. REBECK[3]; [1]Pharmacol. and Physiol., [2]Interdisciplinary Program In Neurosci., [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Amyloid-β (Aβ) plaques are a key hallmark of Alzheimer's Disease. Anti-Aβ immunotherapies target Aβ in varying stages of pathology for clearance. One major adverse effect that has been revealed in patients receiving these therapies is Amyloid Related Imaging Abnormalities (ARIA). ARIA reflects edema or hemorrhages at the cerebrovasculature, although most cases of ARIA are asymptomatic. ARIA is significantly more prevalent in APOE4 individuals. The pathophysiological mechanism underlying ARIA is thought to be in part related to cerebral amyloid angiopathy (CAA), which involves the accumulation of Aβ in cerebral blood vessels. The most widely used murine anti-Aβ drug in preclinical research is 3D6. We have treated 5XFAD mice on APOE3 or APOE4 backgrounds (E3FAD and E4FAD, respectively) with 5 mg/kg 3D6 through intravenous injections. We analyzed fixed brain tissues one to ten days later. We observed a significant acute 150% increase in CAA in E4FAD mice over just one to three days, returning to baseline by 10 days. This effect was not seen in E3FAD mice. The 3D6 treatment was associated with a significant 200% increase in microhemorrhages as measured by Prussian Blue staining. This timeframe and genotype difference line up with the symptoms of ARIA, which usually occur within several weeks after the first infusion of anti-amyloid immunotherapy drugs and is more prevalent in APOE4 individuals. We are developing an assay which would allow us to use live imaging to track blood vessels over time, mapping out a time course of CAA formation in each animal. Surgeries are performed on anesthetized head-fixed mice, and a craniotomy hole 3mm in diameter is drilled in the posterior of the skull, keeping the dura intact. A glass cover slip is sealed over the opening, followed by positioning an Inscopix fluorescent camera with a detachable baseplate which is cemented in place. We will visualize blood vessels and amyloid plaques using 70kDa fluorescein dextran and BBBflamma, respectively. The use of smaller fluorescein dextrans would allow us to visualize blood vessel leaks. We hypothesize that blood vessels which acutely gained and lost amyloid will become

structurally compromised. Overall, this research will test the relationship between ARIA and acutely formed CAA after amyloid immunotherapy in our mouse model.

Disclosures: G. Shautidze: None. **P. Pikus:** None. **H. Chehade:** None. **H. Chu:** None. **G.W. Rebeck:** None.

Poster

PSTR087: Alzheimer's Disease: Abeta Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR087.22/S6

Topic:

Support: NIH T32AG071745, Aging and Alzheimer's Research Training Program.

Title: Intravenous anti-Aβ immunotherapy acutely increases cerebral amyloid angiopathy and causes vascular damage preferentially in APOE4 mice

Authors: *P. PIKUS[1], G. SHAUTIDZE[2], G. W. REBECK[3];
[1]Neurosci., Georgetown Univ. Med. Ctr. Interdisciplinary Program In Neurosci., Washington, DC; [2]Pharmacol. and Physiol., [3]Neurosci., Georgetown Univ., Washington, DC

Abstract: Background: High rates of an adverse side effect known as amyloid related imaging abnormalities (ARIA) have presented a challenge in the clinical application of novel anti-Aβ immunotherapies for the treatment of Alzheimer's Disease (AD). Individuals with one or two copies of the APOE ε4 allele are at markedly increased risk for developing ARIA. While risk factors for ARIA including pre-existing cerebral amyloid angiopathy (CAA) are established, there remains no defined mechanism for ARIA or its high rates in APOE4 carriers. **Methods:** We have developed a transgenic mouse model centered on human APOE3 and APOE4 genotype with key features of AD including amyloidosis (5xFAD transgene) and GFP-tagged microglia (Cx3Cr1 promoter). We have treated more than 120 mice intravenously (IV) with a 5mg/kg dose of either 3D6 anti-Aβ immunotherapy or isotype control antibody. Mice are divided into eight groups: APOE4 mice receiving IgG1 control antibody, APOE4 mice receiving 3D6 and euthanized at 24-hours, 72-hours, or 10-days post-treatment, and APOE3 mice divided into the same four groups (N=7-8). We use immunofluorescence, cell sorting, cerebral vessel isolation, ELISA, histology, and MRI to measure plaque clearance, CAA, neuroinflammation, microhemorrhage, vascular integrity, and blood brain barrier permeability at acute timepoints when ARIA occurs most frequently. **Results:** We found a series of acute and significant *APOE4* specific effects. Within 10-days of a single IV dose of 3D6, there was a significant 40% decrease in the number of plaques in regions including the subiculum and thalamus. Within just 24-hours, there was a significant 2-fold increase in total vessels effected by CAA and total CAA deposits in leptomeningeal vessels. We also observed these increases in CAA on ELISA measurements of Aβ40 (2-fold) and Aβ42 (4-fold) from isolated cerebral blood vessels taken from a separate cohort of *APOE4* mice. These increases in CAA correlate with early indications of vascular

damage to alpha-smooth muscle actin and astrocytic endfeet, and 255% increases in microhemorrhage incidence in *APOE4* mice. These increases in microhemorrhages are also observed on in vivo T1*-weighted MRI. **Conclusions:** We show that early Aβ clearance, CAA induction, and the earliest indications of vascular damage occur preferentially in *APOE4* mice. These are novel, previously unrecognized features of CAA formation and ARIA occurring on an acute timeline, when ARIA occurs most often clinically. These *APOE4* specific changes indicate that therapeutic approaches that protect the vasculature during the acute phases of anti-Aβ immunotherapy could have potential to reduce rates of ARIA clinically.

Disclosures: P. Pikus: None. **G. Shautidze:** None. **G.W. Rebeck:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.01/S7

Topic: C.03. Parkinson's Disease

Support: MJFF-022863
PF-SF-JFA-1040267
PF-SSF-941810

Title: Effects of parkinsonian cholinopathy on pedunculopontine response to anesthetic

Authors: *G. H. ZHANG[1], K. C. UDOBI[3], V. ALEMAN[2], R. C. EVANS[4];
[1]Neurosci., Georgetown Univ., Washington, DC; [2]Georgetown Univ., Falls Church, VA; [3]Neurol., Georgetown Univ. Med. Ctr., Washington, DC; [4]Neurosci., Georgetown Univ. Med. Ctr., Washington DC, VA

Abstract: Parkinson's disease (PD) is primarily characterized by the loss of nigrostriatal dopaminergic neurons, making dopamine replacement therapy a common treatment. However, some symptoms are unresponsive to this treatment, including balance dysfunction, postural instability, and freezing of gait. Instead, these deficits have been tied to cholinergic neuron degeneration in the pedunculopontine nucleus (PPN). The PPN is a heterogeneous midbrain structure, comprising of cholinergic, glutamatergic, and GABAergic neuronal populations that help regulate sensory processing and sensorimotor integration. It also plays an important role in arousal and wakefulness through extensive connectivity within the ascending reticular activating system. Anesthesia acts on and disrupts this system, acting as an agonist for inhibitory GABA and glycine receptors, while blocking excitatory glutamate. To determine how sensory processing in the PPN may be affected by the degeneration of local cholinergic neurons and exposure to anesthesia, we utilized a novel lesion PD model using a Cre-dependent caspase to selectively degenerate cholinergic PPN neurons and examined local cellular excitability with in vivo fiber photometry and the calcium sensor, GCaMP. Mice were monitored awake and at three different depths of anesthesia. Our results show a notable difference in response to visual stimuli

between lesion and control mice while awake. Moderate differences are also seen between the two groups during auditory and vestibular stimuli. This suggests cholinergic neurons play a modulatory role for local glutamatergic activity, particularly with visual input. We also observe significant dampening of glutamatergic PPN activity with anesthetic exposure, though lesion mice appear to be slightly resistant to the anesthetic effects, which may relate to why PD patients face increased risk for complications under anesthesia. Overall, these results provide valuable insight into the viability of the PPN as a target for new innovative therapies for PD, ultimately with the goal of improving quality of life and reducing anesthetic complications for those with PD.

Disclosures: G.H. Zhang: None. **K.C. Udobi:** None. **V. Aleman:** None. **R.C. Evans:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.02/S8

Topic:

Support: T32AG071745
MJFF-022863
PF-SF-JFA-1040267
PF-SSF-941810
T32NS041218
GT17029

Title: Basal ganglia circuit alterations resulting from loss of brainstem cholinergic neurons

Authors: *V. LEWITUS[1], M. BEAVER[2], L. RUSS[2], K. C. UDOBI[3], M. FALLAH[3], B. J. BERNSTEIN[3], S. ZHANG[3], G. ZHANG[3], P. BOMMAREDDY[3], J. WALKER JR[3], V. ALEMAN[3], R. C. EVANS[3];
[1]Neurosci., Georgetown Univ., Washington, DC; [2]Pharmacol. and Physiol., [3]Neurosci., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Parkinson’s disease (PD) is one of the most common neurodegenerative disorders, characterized by debilitating motor impairments. While the most well-studied brain region that degenerates in PD is the substantia nigra pars compacta (SNc), PD also features the death of the cholinergic neurons of a brainstem region called the pedunculopontine nucleus (PPN). Very little is known about the functional consequences of PPN cholinergic degeneration, including its effects on the broader neural circuitry known to be dysregulated in PD, in particular the SNc and the dorsal striatum. To examine the progression of PPN glutamatergic circuit alterations resulting from PPN cholinergic neuron loss, we selectively lesioned PPN cholinergic neurons in mice and performed *ex-vivo* whole-cell patch clamp electrophysiology in conjunction with optogenetic stimulation of PPN glutamatergic axons in the SNc and dorsal striatum. In the SNc, we find a

lesion-induced increase in NMDA receptor-mediated slow excitatory currents selectively in the more vulnerable, ventral tier SNc subpopulation. We also find alterations in the intrinsic properties of dorsal striatal cholinergic interneurons (CINs) that differ by subregion: in the dorsomedial striatum, CINs exhibit reduced excitability in the presence of the lesion. In the dorsolateral striatum, CINs exhibit heightened dendritic complexity. Together, these results indicate that PPN cholinergic neuron degeneration leads to notable changes in key neuronal populations in motor circuitry. These changes may in turn contribute to increased vulnerability to PD degeneration in the SNc and altered cholinergic and dopaminergic tones in the dorsal striatum.

Disclosures: V. Lewitus: None. **M. Beaver:** None. **L. Russ:** None. **K.C. Udobi:** None. **M. Fallah:** None. **B.J. Bernstein:** None. **S. Zhang:** None. **G. Zhang:** None. **P. Bommareddy:** None. **J. Walker Jr:** None. **V. Aleman:** None. **R.C. Evans:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.03/T1

Topic:

Support: BRAIN Initiative K99/R00 award R00NS112417
Michael J. Fox Foundation grant MJFF-028459

Title: Chronic nicotine reduces nigral dopaminergic activity and remodels pedunculopontine cholinergic subpopulations

Authors: *R. Y.-T. CHEN, H. HOSSEINI, R. C. EVANS;
Neurosci., Georgetown Univ. Med. Ctr., Washington DC, DC

Abstract: Nicotine has been linked to reduced risk of Parkinson’s disease (PD), yet the cellular mechanisms underlying its neuroprotective effects remain unclear. While most studies have focused on substantia nigra pars compacta (SNc) dopaminergic neurons, PD also involves degeneration of pedunculopontine nucleus (PPN) cholinergic neurons. Moreover, because PD is an age-related disorder, it is critical to understand the effects of nicotine in adult animals. Here, we administered chronic oral nicotine or vehicle (0.2% saccharin) to adult mice of both sexes (median age ~6 months) for 8-10 weeks across 20 independent cohorts. Vehicle control and nicotine-treated animals were matched for sex, age, and litter within each cohort. We performed whole-cell patch-clamp electrophysiology, two-photon calcium imaging, and dendritic reconstruction using acute brain slices to examine functional and morphological adaptations in SNc dopaminergic and PPN cholinergic neurons. Chronic nicotine reduced spontaneous pacemaking frequency, burst propensity, and rebound firing in SNc dopaminergic neurons (N = 12 control/12 nicotine animals, n = 36/37 cells), while decoupling tonic firing rate from proximal dendritic calcium influx. These changes occurred without alterations in L-type calcium channel

contributions, dendritic arborization, or excitatory synaptic drive. In PPN cholinergic neurons, nicotine induced subregion-specific plasticity: rostral neurons (N = 9/13, n = 26/36) exhibited depolarized membrane potentials, broadened action potentials, and dendritic pruning, whereas caudal neurons (N = 10/13, n = 32/29) showed reduced spike frequency adaptation and accelerated excitatory postsynaptic current kinetics. Together, these findings reveal that chronic nicotine produces targeted, cell type-specific, and subregion-specific changes in two brainstem populations vulnerable in PD. While the electrophysiological properties and calcium influx reduced by chronic nicotine in SNc dopaminergic neurons are known contributing factors to PD vulnerability, the functional adaptations in PPN cholinergic neurons may reveal novel mechanisms by which chronic nicotine alters brainstem information processing in drug dependence and other brain disorders.

Disclosures: R.Y. Chen: None. **H. Hosseini:** None. **R.C. Evans:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.04/T2

Topic:

Support: MJFF-022863
PF-SF-JFA-1040267

Title: Brainstem cholinergic cell loss induces mild motor, but not non-motor, Parkinsonian symptoms.

Authors: *V. ALEMAN[1], R. C. EVANS[3], K. C. UDOBI[4], C. KONJA[2], S. GROSSEN[2]; [1]Neurosci., [2]Georgetown Univ., Washington, DC; [3]Neurosci., Georgetown Univ. Med. Ctr., Washington DC, VA; [4]Neurol., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Brainstem cholinergic cell loss induces mild motor, but not non-motor, Parkinsonian symptoms.
By *Valeria Aleman, *Kenea Udobi Ph.D, Christian Konja, Miguel Ezeiza Ortega MSc, SarahGrossen, Rebekah Evans Ph.D.
The pedunculopontine nucleus (PPN) is a midbrain structure implicated in Parkinson’sDisease (PD), particularly in gait, posture, balance and motor control. This structure consists ofcholinergic, glutamatergic, and GABAergic neurons. Cholinergic neurons within the PPN degenerate in PD, but the symptoms related to this degeneration have not been comprehensively isolated. To evaluate motor and non-motor symptoms caused by brainstem cholinergic cell loss, we developed a novel mouse model using ChAT-cre mice and a cre-dependent caspase system to lesion cholinergic PPN neurons. We find that brainstem cholinergic cell loss impairs balance, but increases locomotion in an open field. Interestingly, these deficits developed weeks after the cholinergic cells should have fully degenerated, indicating secondary circuit adaptations may

play a role in these motor symptoms. Home-cage wheel running was not altered and circadian rhythm remained intact. Similarly, anxiety-like behaviors and novel object memory were unaffected. Indeed, all tested non-motor behaviors were intact. These experiments show that isolated PPN brainstem cholinergic cell loss causes motor symptoms similar to those seen in early-stage PD, but does not induce substantial non-motor impairments.

Disclosures: V. Aleman: None. **R.C. Evans:** None. **K.C. Udobi:** None. **C. Konja:** None. **S. Grossen:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.05/T3

Topic:

Support: Michael J Fox Foundation - MJFF-022863
Parkinson's Foundation - PF-SF-JFA-1040267

Title: Influence of pedunculopontine nucleus cholinergic degeneration on PPN glutamatergic sensory processing

Authors: *K. C. UDOBI[1], G. ZHANG[3], V. ALEMAN[4], R. C. EVANS[2];
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Abstract: The pedunculopontine nucleus (PPN) is a brainstem structure at the intersection of sensorimotorcircuitry and is important for sensory processing. The cholinergic neurons in this structure degenerate in Parkinson’s disease (PD). We have developed a novel mouse model of PPN cholinopathy using a cre-dependent caspase injected into the PPN of ChAT-cre mice. These mice have slowly-developing mild behavioral impairments and circuit connectivity aberrations. To test the effects of this cholinergic cell loss on PPN sensory processing, we use fiber photometry to measure PPN glutamatergic activity during sensory stimuli (visual, auditory, and vestibular) in control and cholinopathy conditions. We find that PPN glutamatergic neurons respond with strong, but transient activation to changes in ambient room lighting, high frequency sound pulses, and vestibular stimulation. We are evaluating whether the presence or absence of PPN cholinergic neurons alters these PPN glutamatergic responses. This study illuminates the intricate interplay between cholinergic PPN degeneration and PPN sensorimotor processing, providing a valuable framework for expanding our knowledge of PD cholinopathy.

Disclosures: K.C. Udobi: None. **G. Zhang:** None. **V. Aleman:** None. **R.C. Evans:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.06/T4

Topic: C.03. Parkinson's Disease

Support: Department of Defense Grant HT9425-24-1-0626

Title: Investigating the role of raphe-cortical serotonin in L-DOPA-induced cognitive impairments and psychosis in a rat model of Parkinson's disease

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Abstract: Parkinson's disease (PD) is caused by the loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc). Nearly all PD patients experience a myriad of nonmotor symptoms (NMS). Cognitive impairments and psychosis (CIP) are among the most common and deleterious NMS, with over 80% of patients developing PD dementia (PDD) and 75% of patients developing significant hallucinations and delusions within 20 years of diagnosis. Unfortunately, the neural substrates of CIP are enigmatic, and treatment options remain limited. Moreover, CIP can be induced or exacerbated by the most effective treatment for PD, DA replacement therapy with levodopa (L-DOPA), with motor and nonmotor fluctuations corresponding to active ("ON") and withdrawal ("OFF") phases of L-DOPA treatment. That CIP may be exacerbated by L-DOPA is of great interest as our prior work studying motor side effects of L-DOPA has implicated compensatory neuroplasticity within the dorsal raphe nucleus (DRN) originating serotonin (5-HT) system. Accumulating evidence suggests that both DA denervation and L-DOPA treatment reorganize 5-HT circuits in the prefrontal cortex (PFC). Given that 5-HT and DA signaling in the PFC is involved in the manifestation of visual hallucinations and cognitive flexibility, it is likely that these domains are sensitive to disease and treatment-related changes in 5-HT nonmotor circuits. Thus, we predicted that lesion and L-DOPA-induced changes drives late-stage CIP symptom development. To test this, male and female Long Evans rats expressing the Cre transgene in tryptophan-hydroxylase 2 (TPH2) positive neurons received unilateral 6-hydroxydopamine or sham lesions to the left medial forebrain bundle before receiving infusions of a retrograde Cre-dependent AAV containing an inhibitory DREADD (pAAV-hSyn-DIO-hM4D(Gi)-mCherry) or control (pAAV-hSyn-DIO-mCherry) into the mPFC. Animals were then co-treated with L-DOPA or Vehicle (VEH.) and the DREADD ligand, Compound 21 (C21), or VEH for 14 days before undergoing a battery of "ON" and "OFF" treatment motor and nonmotor tests to assess motor performance, L-DOPA-induced dyskinesia, neuropsychiatric symptoms, and cognitive flexibility. We hypothesized that L-DOPA-induced 5-HT neuroplasticity related to cognitive and sensorimotor dysfunction will be blocked by chronic chemogenetic inhibition of the DRN-to-PFC circuit. Behavioral data indicate domain specific induction of CIP behaviors correspondent with lesion, L-DOPA, and DREADD conditions, offering a promising avenue for the identification of druggable targets within the nonmotor circuits of the 5-HT system.

Disclosures: G. McManus: None. **F.P. Manfredsson:** None. **C.R. Bishop:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.07/T5

Topic: C.03. Parkinson’s Disease

Support: ASAP Grant-020572

Title: Progressive LC-NE Neurodegeneration and Circuit Adaptations Underlying Nonmotor Deficits in Parkinsonism

Authors: *W. ZHOU[1], H.-Y. CHU[2];
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Abstract: Parkinson’s disease (PD) is a neurodegenerative disease that exhibits both motor and nonmotor symptoms. While motor symptoms are causally linked with the degeneration of midbrain dopamine neurons, the neurobiological basis of nonmotor symptoms remains poorly understood. We hypothesize that degeneration of locus coeruleus norepinephrine (LC-NE) neurons and the associated circuit dysfunction critically contribute to the manifestation of nonmotor symptoms in parkinsonian state. To test this hypothesis, we generated a genetic mouse model of progressive LC-NE neurodegeneration (i.e., LCI mice) and characterized the motor and nonmotor phenotypes as they age. Here, we report that the LCI mice recapitulated the dying-back, axon-first pattern of neurodegeneration, starting at 8 months of age. Moreover, we demonstrated that numerous morphological and cellular adaptations were triggered in the LC-NE neurons prior to overt cell death. Our ongoing work focuses on characterizing behavioral phenotypes of LCI mice across ages and understanding the underlying neural circuit mechanisms.

Disclosures: W. Zhou: None. **H. Chu:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.08/T6

Topic: C.03. Parkinson’s Disease

Support: PD230123P3
R01NS122226

Title: Role of Dorsal Raphe 5HT Neuronal Activity Mediating the Sensorimotor Gating Deficit in a Rodent Model of Experimental Parkinsonism

Authors: *D. L. SILVA TORRES, E. FLORES-BARRERA, A. CABALLERO, K.-Y. TSENG;
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Abstract: Role of Dorsal Raphe 5HT Neuronal Activity Mediating the Sensorimotor Gating Deficit in a Rodent model of Experimental Parkinsonism
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keywords: experimental parkinsonism, non-motor symptoms, serotonin
Parkison's disease (PD) is characterized by progressive degeneration of midbrain dopaminergic neurons and commonly associated with motor impairments. In addition, PD is also associated with the development of debilitating non-motor deficits including cognitive and emotional dysregulation, anxiety and depression, many of which are similar to those found in psychiatric syndromes with corticolimbic circuit dysfunction. However, the neural mechanisms driving the onset of non-motor deficits remain poorly understood. Here, we used the 6-OHDA rodent model of experimental parkinsonism to investigate the extent to which chronic dopamine lesion impacts the pre-pulse inhibition (PPI) of the acoustic startle response. The PPI construct is a cross-species behavioral measure of sensorimotor gating typically used in neuropsychiatric disorders to assess changes in dysregulation of cognitive and emotional processing. Relative to dopamine-intact rats, animals with dopamine lesion exhibit a significant deficit in the PPI of the acoustic startle response. Given evidence that serotonergic signaling modulates PPI, we conducted ex-vivo electrophysiological recordings and found that dorsal raphe 5HT neurons become hypoactivity following dopamine lesion. We then asked whether direct chemogenetic modulation of dorsal raphe 5HT neuronal activity is sufficient to change PPI levels. Using dopamine-intact Tph2-Cre rats, we found that acute inhibition of dorsal raphe 5HT activity was sufficient to elicit a PPI deficit similar to that observed in 6-OHDA rats. Ongoing experiments will determine the extent to which chemogenetic stimulation of dorsal raphe 5HT neurons restores the PPI deficit found in 6-OHDA rats. Collectively, these results identify a possible mechanistic link between dopamine lesion and the development of a dorsal raphe 5HT hypoactive state driving the onset of non-motor deficits in experimental parkinsonism.
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Disclosures: D.L. Silva Torres: None. **E. Flores-Barrera:** None. **A. Caballero:** None. **K. Tseng:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR088.09/T7

Topic: C.03. Parkinson's Disease

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APDA Grant 1178689
APDA Cotzias Fellowship 1268719
UCLA Laurie and Steven C. Gordon Parkinson's Disease Grant Program
UCLA David Binder Fund for Lewy Body Disease Research

Title: Investigating the effects of modulating corticostriatal circuits on the spread of α-synuclein pathology

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder and is clinically defined by motor features. Nevertheless, PD patients commonly experience cognitive impairments, with 50-80% developing dementia over 10-20 years. Neuropathological studies have demonstrated a correlation between the accumulation of neocortical α-synuclein (α-syn) aggregates, or Lewy pathology, and the likelihood and severity of cognitive impairments in PD. Evidence suggests that α-syn pathology can spread throughout the brain along anatomically connected pathways. However, there is still substantial unexplained variability as to what factor(s) drive vulnerability or resilience to the transmission of α-syn pathology. Some studies have shown that neuronal activity can affect the uptake or release of pathological α-syn. Yet, how changes in the activity of cortical neurons modulate transmission of α-syn pathology to cortical circuits remains unknown. We hypothesize that disrupted activity within cortical circuits will modulate the spread of α-syn pathology to the cortex. In the current study, we injected α-syn pre-formed fibrils (PFFs) into the dorsal medial striatum (DMS) or dorsolateral striatum (DLS), and then used an intersectional strategy to express chemogenetic DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) selectively in corticostriatal (CS) projection neurons from connected cortical regions (primary visual [V1] or motor [M1] cortex, respectively). We expressed either activating (hM3D(Gq)) or inhibiting (hM4D(Gi)) DREADDs, or mCherry controls, and then chronically modulated activity from 1 to 3 months post-PFF-injection (MPI). We then collected brain tissues at either 2 or 4 MPI. Using quantitative immunofluorescence staining, we found that PFF injections induce robust pS129+ α-syn pathology in the striatum with transmission to connected cortical regions. We have also verified proper intersectional DREADD targeting to CS projection neurons. Quantification of cortical α-syn pathology in mice expressing activating and inhibiting DREADDs is in process. We expect that increasing activity in CS projection neurons will lead to faster transmission and/or increased overall burden of α-syn in the cortex and reduce transmission when activity is decreased. This knowledge will be essential for future translational studies investigating neuromodulation (e.g., DBS or TMS) approaches for not just symptomatic, but potentially disease-modifying, therapies for PD.

Disclosures: R. Li: None. **A. Theint:** None. **S. Alhassen:** None. **W. Zeiger:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR088.10/T8

Topic: C.03. Parkinson's Disease

Support: ASAP-020572, H.-Y.C
NINDA/NIH R01NS121371, H.-Y.C

Title: Impaired Local GABAergic Inhibition Promotes Thalamocortical Circuit Dysfunction in Parkinsonism

Authors: *L. CHEN[1], H. CHEHADE[2], S. SOMAVARAPU[1], H.-Y. CHU[3];
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Abstract: Degeneration of dopaminergic (DA) neurons in the substantia nigra (SN) alters the circuit dynamics of the basal ganglia-thalamocortical network, which underlies motor deficits in Parkinson's disease (PD). As the SN DA neurons progressively degenerate, the motor cortex develops an aberrant rate and pattern of neuronal activity in the parkinsonian state. Yet, the molecular and cellular mechanisms underlying cortical dysfunction remain poorly studied.Using the MitoPark mice, a genetic model of Parkinsonism that shows progressive SN DA neurodegeneration and Parkinsonian motor deficits, we conducted longitudinal studies to define cellular and synaptic changes of the primary motor cortex (M1) at different stages of Parkinsonism. Combining ex vivo electrophysiology, optogenetics, retrograde tracing approaches, and behavioral assays, we investigated alterations in intrinsic excitability and thalamocortical transmission of pyramidal tract neurons (PTNs) and intratelencephalic neurons (ITNs) in layer 5 of M1 as SN DA neurons progressively degenerate.We found that PTNs exhibited a progressive reduction in intrinsic excitability and a weakening of excitatory input from the motor thalamus as MitoPark mice gradually developed Parkinsonism. Such changes in cellular excitability and synaptic transmission were not observed in ITNs. Mechanistically, we found that the loss of SN DA neurons induced a selective reduction of inhibitory control of PTNs, but not ITNs, by somatostatin-expressing (SST) interneurons in M1. Furthermore, we found that reduced α5-GABA-A-mediated SST inhibition of PTNs dendrites led to excessive activation of NMDA receptors. Importantly, genetic deletion of the GluN2B subunit of NMDA receptors specifically in PTNs effectively rescued the reduction of AMPAR-mediated thalamo-PT synaptic strength, demonstrating that GluN2B-dependent NMDA receptor signaling is a critical driver of cortical circuit dysfunction in the parkinsonian state.Together, these findings reveal that loss of α5-GABA-A-mediated SST inhibition promotes NMDA receptor overactivation in PTNs, ultimately leading to impaired thalamocortical transmission in PD.

Disclosures: L. Chen: None. **H. Chehade:** None. **S. Somavarapu:** None. **H. Chu:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.11/T9

Topic: C.03. Parkinson’s Disease

Title: Aperiodic Low-Frequency Deep Brain Stimulation Restores Network Dynamics and Improves Cognitive and Motor Performance in a Computational Model of Parkinson's Disease

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Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for motor symptoms in Parkinson’s disease (PD). Although standard DBS suppresses pathological beta synchronization and improves motor function, its effects on cognitive deficits remain inconsistent. Healthy STN activity is characterized by irregular firing and high temporal variability, whereas PD is associated with excessive synchronization, reduced neural variability, and impaired exploratory behavior. We hypothesized that introducing controlled temporal variability into DBS patterns could restore physiological STN-GPe dynamics and improve motor and cognition. We tested this using a computational STN-GPe network model of coupled Izhikevich neurons integrated with reinforcement-learning-based cognitive and motor task frameworks. Neural activity was quantified using entropy and synchrony. We developed an aperiodic low-frequency (40 Hz) biphasic DBS protocol by adding Gaussian-distributed temporal jitter to the stimulation period while maintaining charge balance. The normal network exhibited high entropy and low synchrony, whereas the PD state showed reduced entropy, elevated synchrony, and beta-band oscillations. standard DBS reduced synchrony but produced only modest increases in entropy. In contrast, aperiodic DBS increased entropy and further reduced synchrony, shifting activity toward normal dynamics. These network changes were accompanied by behavioral improvements. In the Iowa Gambling Task (IGT), PD and standard DBS conditions showed impaired performance with negative IGT scores, whereas aperiodic DBS improved scores and decision-making. In a motor reaching task, the PD condition produced tremor-like oscillations near 4 Hz, while both standard and aperiodic DBS reduced tremor and improved reaching performance. Overall, introducing controlled temporal variability through aperiodic low-frequency DBS restored more desynchronized STN-GPe dynamics and improved both motor performance and IGT outcomes in a computational model of PD.

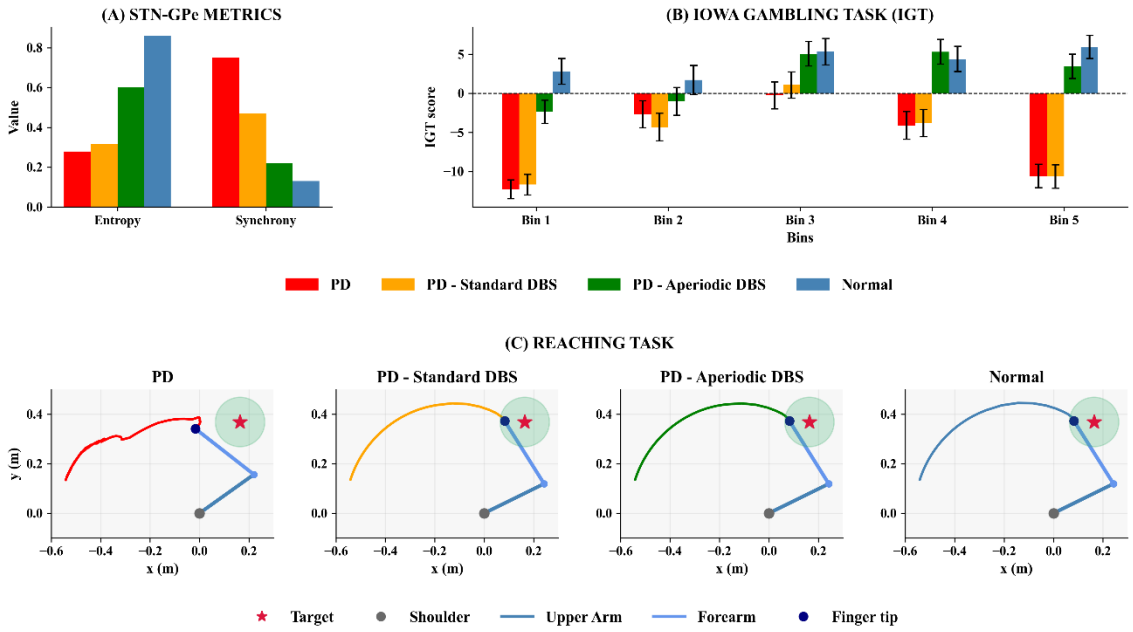


Figure 1. Effects of standard and aperiodic DBS on STN–GPe network dynamics, decision-making, and motor behavior in a computational model of Parkinson's disease. (A) STN–GPe network metrics across conditions. PD network exhibits reduced entropy and elevated synchrony relative to the normal state. Standard DBS partially reduces synchrony with limited restoration of entropy, whereas aperiodic DBS produces a greater increase in entropy and a larger reduction in synchrony toward normal network dynamics. (B) Iowa Gambling Task (IGT) performance measured as IGT score across five task bins. PD and standard DBS conditions show impaired decision-making characterized by predominantly negative net scores. In contrast, aperiodic DBS improves performance across later bins, yielding positive net scores comparable to the normal condition. (C) Representative reaching trajectories for each condition. The PD model exhibits tremor in movement. Both Standard DBS and Aperiodic DBS improved motor behavior relative to PD, showing smoother and more accurate reaching trajectories that closely resemble normal motor control. The green shaded region represents the target radius, and a reach is considered successful when the fingertip enters this region.

Disclosures: S.V. Chakravarthy: None. **C. Palika:** None. **S. Elango:** None. **A. Shreeram:** None. **A. Sharma:** None. **A. Govindaraj:** None. **M. Palsikar:** None. **S. Jillellamudi:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.12/T10

Topic: C.03. Parkinson’s Disease

Support: R01 NS058945
R01 NS110613
Engdahl Family Foundation
MnDRIVE Brain Conditions

Title: Altered motor thalamic neuronal activity is associated with disrupted vigilance in parkinsonism

Authors: Q. FERAGEN[1], A. L. DENICOLA[1], A. VERMA[1], ***L. A. JOHNSON**[3], J. L. VITEK, MD, PHD[2];
[1]Neurol., [2]Dept. of Neurol., Univ. of Minnesota, Minneapolis, MN; [3]Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: The basal ganglia thalamocortical (BGTC) circuit is impaired in Parkinson's disease (PD). The thalamus, a critical node in the BGTC circuit, plays an integral role in regulating sleep/wake cycles via sleep-dependent firing modes. Low Threshold Spike (LTS) bursts are primarily associated with drowsiness/sleep and reduced sensory input. Although PD is typically characterized as a movement disorder, patients commonly experience impaired vigilance and struggle to sustain wakefulness during the day. The neurophysiological mechanisms underlying disorders of vigilance in PD are not well understood.
Previous studies have established a decrease in thalamic mean discharge rates with increased bursting activity in parkinsonism. Most studies, however, did not consider the subject's vigilance state, e.g., awake or asleep, and did not isolate LTS-like bursting activity to determine how the expression of these bursts relate to wakefulness in the PD state. The goal of this study was to determine how the expression of LTS-like bursts changes from normal to increasing parkinsonian severity during periods of wakefulness. We hypothesized that motor thalamic neurons would exhibit increased LTS-like bursting in parkinsonism during wake periods.
Parkinsonism was induced in a nonhuman primate (NHP) via biweekly injections 1-methyl-4-phenyl-1,2,3,6-tetrahydripyridine (MPTP), producing a slow progression from normal to mild and moderate parkinsonian states, defined using clinical rating scores. A Gray Matter Research microdrive was implanted with microelectrodes targeting the motor thalamus. Eye video was recorded to determine vigilance i.e., eye-open (awake) or eye-close (sleep) periods. Following single-unit spike sorting, LTS-like bursts were characterized as containing three or more spikes, initial inter-spike interval (ISI) up to 5ms, final ISI of no more than 10ms, and a quiescent period of 100ms.
We observed a progressive decrease in wakefulness ($p<0.001$) as the subject transitioned from normal to mild and moderate parkinsonian states. We also noted a significant progressive increase in the expression of LTS-like bursts ($p<0.001$) and an increase in burst incidence ($p<0.001$) from normal to mild and moderate parkinsonian states. These changes were expressed in the absence of firing rate changes. Furthermore, in parkinsonism we observed a reduction in the eyes-open vs eyes-closed decoding accuracy using the patterns of burst activity in the motor thalamus as a feature. Our data suggests that neurons in the motor thalamus exhibits sleep-like behavior during wake in parkinsonism and may contribute to disruption in vigilance observed in PD.

Disclosures: Q. Feragen: None. **A.L. DeNicola:** None. **A. Verma:** None. **L.A. Johnson:** None. **J.L. Vitek, MD, PhD:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

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Topic: C.03. Parkinson's Disease

Support: National Key Research and Development Program of China (2022YFC2405100)

Title: Chronic and adaptive STN-DBS reveal multi-timescale mechanisms underlying sleep regulation in Parkinson's disease

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Abstract: Sleep is regulated across multiple temporal scales, yet the neural mechanisms governing sleep organization and state transitions remain unclear. Sleep disturbances are common in Parkinson's disease (PD), and their improvement with subthalamic nucleus deep brain stimulation (STN-DBS) provides a unique opportunity to probe the neural mechanisms of sleep regulation in humans. To address this question, we combined longitudinal follow-up assessments with sleep stage-specific closed-loop stimulation in patients implanted with sensing-enabled STN-DBS systems. Eight participants were followed across five time points over one year, and six subsequently completed 24-h NREM-, REM-, and combined NREM-REM-triggered stimulation experiments. At the overnight timescale, chronic DBS significantly improved sleep continuity, with arousal index decreasing from 16.3±10.1 to 10.5±5.7 events/h over the 1-year follow-up ($\beta = -0.730$, $p<0.01$). This improvement was associated with enhanced NREM sleep stability, reflected by increased cortical spindle activity (both amplitude and duration, $p<0.01$) and reduced NREM beta oscillations, as well as reorganization of REM sleep microstructure, characterized by increased phasic REM expression ($p<0.001$) and reduced REM gamma activity. Together, these coordinated cortical-STN changes suggest long-term remodeling of sleep-related neural networks. At the sleep-state timescale, adaptive DBS primarily influenced sleep-state transitions rather than conventional sleep architecture. NREM-triggered stimulation reduced total REM duration by 25.5%, primarily through a reduction in tonic REM duration while preserving phasic REM expression, consistent with altered REM-state maintenance. In parallel, REM-triggered stimulation stabilized NREM sleep, decreasing N2→Wake/N1 transition probability from 8.4% to 6.1%. Combined NREM-REM stimulation further stabilized deep sleep by reducing N3→Wake/N1 transition probability from 3.58% to 0%. Consistent with these state-specific effects, EEG-LFP-based HMM analyses revealed redistribution of latent neural states and altered transition patterns, supporting modulation of sleep-state dynamics. These findings support a multi-timescale model of DBS-mediated sleep regulation, in which chronic stimulation remodels sleep-related neural networks across the overnight timescale, whereas adaptive stimulation modulates sleep-state dynamics at the level of ongoing state transitions.

Disclosures: Y. Liu: None. **G. Zhang:** None. **L. Guan:** None. **Y. Fan:** None. **Y. Wu:** None. **H. Tian:** None. **H. Yu:** None. **L. Li:** None.

Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

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Program #/Poster #: PSTR088.14/T12

Topic: C.03. Parkinson's Disease

Support: PAPIIT (DGAPA-UNAM) 200126
SECIHTI CVU 1036962
SECTEI/114/2022

Title: Dopamine depletion induces persistent, cell-type-specific disruptions in striatal interneuron network dynamics

Authors: *A. FUENTES-SERRANO[1], M. PADILLA[2], E. LARA-GONZALEZ[3], M. DUHNE[4], A. LAVILLE[1], H. A. VÁZQUEZ VÁZQUEZ[1], Y. PARRADO[1], E. GALARRAGA[1], J. BARGAS[1];
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Abstract: Striatal hyperactivity is a well-established feature of the Parkinsonian state, yet the precise functional imbalances within striatal projection neurons (SPNs) that generate this feature remain a subject of debate. How distinct interneuron populations behave during parkinsonism is poorly understood, despite their vital role in modulating microcircuit output. To address this, we utilized calcium imaging in a minimal ex vivo preparation from transgenic mice of both sexes to track the spontaneous population dynamics of five microcircuit components with the lowest confounds: direct and indirect pathway SPNs, cholinergic interneurons (CINs), somatostatin-expressing (SST+) interneurons, and parvalbumin-expressing (PV+) interneurons. Neuronal activity was evaluated across control, dopamine (DA)-depleted, and L-DOPA-treated conditions. DA depletion disrupts firing dynamics across all evaluated populations. Divergent responses in SPNs confirmed the classical model. In addition, we report that the activity of both SST+ and PV+ GABAergic interneurons is severely suppressed, a phenomenon that likely contributes to striatal hyperactivity. Concurrently, CINs displayed enhanced activity and aberrant firing patterns. Notably, L-DOPA administration failed to restore the suppressed activity of GABAergic interneurons to control levels, revealing alterations in striatal microcircuit organization that persisted after medication. These circuit alterations offer new insights into the therapeutic limitations and side effects of dopamine-replacement therapy, highlighting the critical need to explore alternative pharmacological targets.

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Poster

PSTR088: Parkinson's Disease: Circuit Mechanisms in Model Organisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR088.15/T13

Topic: C.03. Parkinson's Disease

Title: Reduced motor cortical multiscale entropy in Parkinsonian rats

Authors: *J. S. LARRATT, R. E. HARTMAN;
Loma Linda Univ., Loma Linda, CA

Abstract: Beta power is used in deep brain stimulation (DBS) and closed-loop DBS approaches for Parkinson's disease, but spectral power alone does not account for changes in neural temporal complexity. This study examined whether multiscale entropy (MSE), a measure of signal irregularity across different time scales, provides complementary information about motor cortical dysfunction in a rat model of Parkinson's disease. We analyzed a publicly available longitudinal electrophysiology dataset including sham-lesioned rats, unilateral 6-hydroxydopamine "hemi-Parkinsonian" rats (PD), and hemi-Parkinsonian rats receiving DBS (PD-DBS) with an additional five days of closed-loop DBS. Local field potentials from layer V of lesion/matched-side primary motor cortex (M1) were detrended, bandpass filtered from 0.5–100 Hz, notch filtered at 50 and 100 Hz, and analyzed across weeks 2–5 during sleep, wake, and walking states. For closed-loop DBS files from days 29-33, artifacts were removed using threshold-based detection and interpolation before downsampling and LFP filtering. MSE was calculated across 20 MSE scale factors using 30-s windows with sample entropy parameters m = 2 and r = 0.15 × window SD, followed by subject-level aggregation. MSE values were analyzed using mixed-effects models with subject as a random intercept and fixed effects of group, week, day, behavioral state, scale or scale-band, beta-power and stimulation day for closed-loop DBS analyses. Results showed entropy in M1 was higher in sham rats than in both Parkinsonian groups, which did not differ significantly. Beta power negatively predicted entropy ($\beta = -0.124$, $p < .001$). However, even in beta-adjusted models, entropy remained higher in sham rats than in PD ($\beta = -0.253$, $p < .001$) or PD-DBS rats ($\beta = -0.246$, $p < .001$), which did not differ. The effects were largest at smaller (finer) scales 1-5 (sham > PD: $d = 1.24$; sham > PD-DBS: $d = 1.26$) and medium (coarser) scales 6-12 (sham > PD: $d = 0.81$; sham > PD-DBS: $d = 0.82$). Entropy was higher during wake ($\beta = 0.049$, $p < .001$) and walking ($\beta = 0.082$, $p < .001$) relative to sleep. However, group differences were not significantly moderated by behavioral state. During stimulation days, beta power also negatively predicted entropy ($\beta = -0.234$, $p < .001$). These findings suggest that MSE may provide an index of motor cortical dysfunction in Parkinsonian rats that provides information related to, but not redundant with, beta-band power.

Disclosures: J.S. Larratt: None. **R.E. Hartman:** None.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.01/T14

Topic: C.03. Parkinson's Disease

Support: Parkinson's Foundation Summer Student Fellowship
Brain Research Foundation, Seed Grant

Title: Identifying a Novel Enhancer Regulating Neural Resilience to Parkinson's disease

Authors: *A. BURETTA[1], H. KIM[1], F. D. ROGERS[1], R. LIN[2], M. DEBERARDINE[3], K. SULLIVAN[2], C. J. PENA[1];
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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder and causes loss of dopaminergic neurons primarily in the substantia nigra (SNc). Interestingly, degeneration across the SNc is not uniform, as a small subpopulation of dopaminergic neurons that co-transmit glutamate (DA-VGLUT2 neurons) remain resilient to Parkinson's disease in both humans and PD-mouse models. These neurons co-express the vesicular glutamate transporter 2 (VGLUT2), which undergoes dynamic changes in expression throughout the lifespan. The majority of mouse DA neurons co-express VGLUT2 in utero but many lose this ability later in life. However, this DA-VGLUT2 identity re-emerges in some DA neurons after 6-OHDA exposure and may contribute to disease resilience. While heterologous overexpression of Slc17a6 is paradoxically toxic, we hypothesized that promoting VGLUT2 expression or activating DA-VGLUT2 neurons through cell-type-specific enhancers may confer resilience. Using single-nucleus multiome-sequencing from nearly a quarter-million midbrain cells across development, we identified five DA-VGLUT2-specific enhancers. We then developed YFP-tagged enhancer-driven AAVs for in vivo identification of the top enhancer specific to this resilient subpopulation. Using RNAscope, we validated an enhancer that was specific to this cell type, which now enables us to track its epigenetic profile across disease progression and develop novel genomic tools. Together, our work has identified a novel enhancer that may regulate PD resilience in dopaminergic neurons, representing an exciting new therapeutic target for this disease.

Disclosures: A. Buretta: None. **H. Kim:** None. **F.D. Rogers:** None. **R. Lin:** None. **M. DeBerardine:** None. **K. Sullivan:** None. **C.J. Pena:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Autobahn Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Autobahn Therapeutics. F. Consulting Fees (e.g., advisory boards); Autobahn Therapeutics.

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PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.02/T15

Topic: C.03. Parkinson’s Disease

Support: PDF PF-RCE-1948

Title: Regional multi-omic analysis reveals distinct glial programs across brain regions in Parkinson's disease

Authors: *A. YADAV[1], Z. CHATILA[1], V. MENON[2], S. E. PRZEDBORSKI[1];
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Abstract: Parkinson's disease (PD) is characterized by progressive neurodegeneration, however, the mechanisms underlying selective regional vulnerability remains poorly understood. While loss of dopaminergic neurons in the substantia nigra (SN) is a hallmark of PD, glial cells are now increasingly recognized as key contributors to disease progression. In order to investigate region-specific glial changes, we performed single-nucleus RNA-seq and ATAC-seq on 157 postmortem samples from 28 PD and 18 control donors across four brain regions exhibiting differing degrees of PD pathology: the SN, ventral tegmental area (VTA), substantia innominata (SI), and hypothalamus.We have uncovered interesting disease and region associated heterogeneity across microglia, astrocytes, and oligodendrocytes. Astrocytes exhibited widespread inflammatory activation and loss of homeostatic programs in PD, along with region-specific reactive and metabolic states enriched in vulnerable midbrain regions. We also observed some SN-specific neuroprotective states in Astrocytes depleted in PD. Oligodendrocytes displayed distinct regional signatures, including axon-support and extracellular matrix remodeling programs enriched in the VTA and stress-responsive states that increased broadly in PD. Within the myeloid compartment, we identified a $CD83^{+}$/$BCAS2^{+}$ microglial population enriched for neuroprotective and stress-response pathways that was selectively depleted in the PD SN.Together, these findings reveal localized glial remodeling across the PD brain regions and highlight region-specific cellular programs that could contribute to differential pathology and progression of Parkinsons Disease.

Disclosures: A. Yadav: None. **Z. Chatila:** None. **V. Menon:** None. **S.E. Przedborski:** Other; Reviewing Editor for eLife and Scientific Board Member of Luciole Pharmaceuticals, Inc..

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

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Program #/Poster #: PSTR089.03/T16

Topic: C.03. Parkinson’s Disease

Support: NRF Grant RS-2025-25426683

Title: Investigation of dopaminergic neuron recovery by gut bacterial genes regulating methylglyoxal metabolism in a Parkinson’s disease model

Authors: *D. YOO[1,2,3], E. LEE[1,2,3], M. KIM[4];
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Abstract: <META NAME="author" CONTENT="다영 유">**Investigation of dopaminergic neuron recovery by gut bacterial genes regulating methylglyoxal metabolism in a Parkinson's disease model**
Authors *Dayeong YOO[1,2], Min-Gi Shin[1], Eun Jeong Lee[1,2]; [1]Department of Biomedical Sciences, Ajou University School of Medicine, Suwon, Republic of Korea; [2]Department of Biomedical Sciences, Graduate School of Ajou University, Suwon, Republic of Korea
Disclosures Dayeong YOO: None. **Min-Gi Shin:** None. **Eun Jeong Lee:** None.
Abstract Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra (SN). Although the etiology of PD remains incompletely understood, increasing evidence suggests that gut microbiota contribute to PD pathogenesis. In our previous metagenomic analyses, *hns* (histone-like-nucleoid-structuring protein) was enriched in the fecal microbiota of patients with PD. Furthermore, deletion of *hns* in *E. coli* reduced the production of methylglyoxal (MG), a pathogenic factor associated with dopaminergic neurodegeneration (Shin et al., 2020). In addition, our previous metagenomic analysis revealed altered expression of multiple gut microbial genes involved in MG metabolism in the fecal microbiota of patients with PD, among which six genes (*mgsA, dld, lldD, hchA, gloB/C, aldA*) were enriched in PD patients and selected as candidates for functional analysis together with *hns* (Park et al., 2024). Based on these observations, we hypothesized that modulation of microbial genes involved in MG metabolism may alter PD pathology through effects on host dopaminergic neurons. To investigate this possibility, we employed the KEIO collection to screen these candidate genes. Knockout strains were fed to UA44 *C. elegans* expressing human α-synuclein, and dopaminergic neuron integrity was assessed by confocal microscopy at days 3 and 5 of adulthood ($n \approx 30$ worms per condition, 3 independent experiments, two-way ANOVA). *Δhns* exhibited the strongest rescue of dopaminergic neurodegeneration. Notably, deletion of *mgsA*, a key MG biosynthetic enzyme, also significantly improved neuronal integrity ($P < 0.05$). In contrast, deletion of the remaining five genes did not confer significant neuroprotective effects. Collectively, our findings identify *hns* and *mgsA* as candidate microbial regulators of neurodegeneration and suggest that specific microbial genes involved in MG metabolism contribute to PD pathology through MG-related mechanisms. These results provide insights into gut microbiota–host interactions and identify microbial metabolic pathways as therapeutic targets for PD.

Disclosures: D. Yoo: None. **E. Lee:** None. **M. Kim:** None.

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PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.04/T17

Topic: C.03. Parkinson's Disease

Support: Italian Ministry of University and Research

Title: p75NTR Pharmacological modulation via LM11A-31 Counteracts Rotenone-induced Alterations in a Microglial Cell Model of Parkinson's Disease

Authors: A. VALENZA[1], D. PENSABENE[3], F. RENDINA[1], M. MUZZI[2], A. FRACASSI[5], M. SEGATTO[4], *S. MORENO[2];
[1]Univ. Roma Tre, Roma, Italy; [2]Univ. Roma Tre, Rome, Italy; [3]Univ. of Molise, Cassino, Italy; [4]Univ. of Molise, Pesche (IS), Italy; [5]Mitchell Ctr. for Neurodegenerative Diseases, Dept. of Neurol., Univ. of Texas Med. Br., Galveston, TX

Abstract: Parkinson's disease (PD) is characterized by progressive nigrostriatal dopaminergic degeneration, mitochondrial dysfunction, protein misfolding and chronic neuroinflammation. Microglia actively shape disease progression, although they normally preserve central nervous system homeostasis through immune surveillance and debris clearance. Indeed, persistent toxicity can redirect them toward a reactive phenotype that enhances ROS production, cytokine release and neuronal vulnerability. Neurotrophins signaling is increasingly linked to PD pathophysiology, however, the contribution of low-affinity neurotrophin receptor p75 (p75NTR) to microglial dysfunction remains unclear. As p75NTR balances survival and apoptotic processes, we explored whether its pharmacological modulation via LM11A-31 could protect BV2 microglial cell line from rotenone (Rot)-induced toxicity, a model of PD-related mitochondrial impairment. Rot increased p75NTR expression ($p<0.05$ *vs.* Ctrl), reduced cell number and promoted apoptotic damage, as indicated by increased $TUNEL^+$ cells and cleaved Caspase-3 immunoreactivity ($p<0.0001$ *vs.* Ctrl). Such alterations were counteracted by LM11A-31 ($p<0.0001$ *vs.* Rot), which also preserved cell ultrastructure and α-tubulin organization. Consistently, Rot drove microglia toward a reactive phenotype, increasing IBA1, CD68, cell area, IL-6 and TNF-α, whereas LM11A-31 markedly reduced this inflammatory profile ($p<0.05$ to $p<0.0001$ *vs.* Rot). In parallel, Rot also promoted a pro-oxidant microglial state, marked by $NOX4/p47^{PHOX}/p22^{PHOX}$ upregulation and increased BODIPY-detected lipid peroxidation ($p<0.05$ to $p<0.0001$ *vs.* Ctrl). This oxidative profile was significantly attenuated by LM11A-31, which reduced NOX-associated signals and lipid oxidative damage ($p<0.05$ to $p<0.0001$ *vs.* Rot). Rot disrupted redox homeostasis, triggering NRF2 and PPARα activation despite weakened downstream antioxidant defenses, including reduced SOD1, GPx1 and glutathione synthetase, and increased glutathione reductase ($p<0.05$ to $p<0.001$ *vs.* Ctrl). LM11A-31 restored this imbalance by normalizing NRF2- and PPARα-dependent signaling, rescuing SOD1 and GPx1, and increasing GSH immunoreactivity ($p<0.05$ to $p<0.001$ vs Rot), consistent with reinforced glutathione-dependent protection. Overall, LM11A-31 protects microglia from Rot-induced cytotoxicity through p75NTR modulation, limiting apoptosis and inflammatory activation while preserving redox homeostasis. These findings support p75NTR targeting as a promising strategy against microglia-mediated mechanisms in PD.

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Topic: C.03. Parkinson's Disease

Support: NIH Grant F30NS141487
NIH Grant R01NS115809

Title: Estrogen-dependent upregulation of endoplasmic reticulum exit sites mediates protection against dopaminergic neuron loss in a mouse model of Parkinson's disease

Authors: *R. C. GARCIA[1], G. PANDEY[4], L. KUNAM[2], M. ZENEBE[2], R. SRINIVASAN[3]; [1]Neurosci. and Exptl. Therapeut., [2]Texas A&M Univ. Naresh K Vashisht Col. of Med., Bryan, TX; [3]Dept. of Neurosci. and Exptl. Therapeut., Texas A&M Univ. Naresh K Vashisht Col. of Med., College Station, TX; [4]Texas A&M Univ. Inst. For Neurosci., Bryan, TX

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide and is characterized by progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). Endoplasmic reticulum (ER) stress, driven by the accumulation of unfolded and misfolded proteins, contributes significantly to DA neuron degeneration and represents a promising therapeutic target. Our previous studies demonstrated that cytisine, a smoking cessation drug and neuronal nicotinic acetylcholine receptor (nAChR) agonist, acts as a pharmacological chaperone of nAChRs which reduces ER stress and promotes formation of Sec24D-containing ER exit sites (ERES) in DA neurons. Furthermore, we have recently found that cytisine treatment or a novel mutation inducing constitutive upregulation of β2-containing nAChRs increases Sec24D-ERES formation and confers neuroprotection in female, but not male, mice in a 6-hydroxydopamine (6-OHDA) model of PD. Our recent work has also established that circulating 17β-estradiol is critical for ERES upregulation and consequent neuroprotection. Therefore, we hypothesized that treatment of constitutively β2-nAChR-upregulated male mice with the brain-selective estrogen prodrug DHED would mediate ERES upregulation and confer neuroprotection in a 6-OHDA PD model. After testing this, we found that DHED treatment did not alter Sec24D-ERES number, however, it significantly increased Sec24D intensity within individual ERES, suggesting estrogen-dependent remodeling of ERES structure rather than increased ERES formation. This remodeling of existing ERES was associated with protection against DA neuron loss in male 6-OHDA PD mice. Moreover, analysis of the autophagy markers LC3B, p62, and LAMP1 revealed enhanced autophagic flux in DHED-treated DA neurons, suggesting that increased degradative capacity contributes to this neuroprotective effect. In summary, these findings indicate that 17β-estradiol acts in concert with nAChR upregulation to promote ERES remodeling, enhance autophagic flux, and protect DA neurons from degeneration. Taken together, the results of this study highlight estrogen-dependent regulation of DA neuron ERES structure as a potential neuroprotective strategy for PD.

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PSTR089: Therapeutic Strategies for Parkinson's Disease

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Program #/Poster #: PSTR089.06/T19

Topic: C.03. Parkinson's Disease

Title: Features of rotenone-induced neural impairment and protective effects of aromatic vanilloids.

Authors: *A. MATSUSHITA[1], A. MENA ACRA[2,3], K. KAWAGUCHI[1], H. SATO[1], H. SAKAGAMI[3], K. ADACHI[1];
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Abstract: Severe mitochondrial damage leads to neurodegeneration (e.g., Parkinson's disease (PD)). Although the critical damage resulted in cell death, the morphological/functional alterations should be induced first. In this study, features altered prior to rotenone (a mitochondrial respiratory complex I inhibitor)-induced cell death were evaluated in PC12 cells as a prodromal PD *in vitro* model. Recently, we reported the protective effects of aromatic vanilloids in cell death of human dermal fibroblasts. The aims of this study were: 1. to confirm the alterations prior to cell death would serve as effective indices for further investigation, 2. to evaluate protective effects of aromatic vanilloids on such pre-cell death features. PC12 was differentiated by treatment with NGF (10 ng/mL) for 7 days, then exposed to rotenone (0, 100, 300, 500 nM) for 24 hours. To measure protective effects of vanillin (10, 50 μM), vanillic acid (10, 50 μM), or N-acetyl-L-cysteine (NAC: 1 mM) were treated 2 hours prior to rotenone treatment. Cell viability and morphological alterations were evaluated by phase-contrast microscopy. ROS production, mitochondrial membrane potential (MMP), ATP level, and Annexin V-FITC fluorescence were also measured. In the rotenone-treated group, PC12 showed a concentration-dependent decrease in cell viability, the longest neurite length, primary neurite number, neurite-bearing cell number, and intracellular ATP level compared to the untreated group. ROS production and Annexin V-FITC fluorescence also increased in a rotenone concentration-dependent manner. In particular, 300 nM rotenone treatment induced significant neurite shortening, decrease in primary neurite number, and reduction in neurite-bearing cell number without excessive cell death. All features altered by rotenone were protected by pretreatment with NAC. Pretreatment with vanillin partially inhibited the rotenone-induced decrease in cell viability at both concentrations, particularly protecting the longest neurite length and primary neurite number in neurite-bearing cells. Vanillic acid showed a similar effect at 50 μM, but its effect at 10 μM was limited. Both compounds also inhibited the rotenone-induced increase in ROS and Annexin V-FITC fluorescence, and the decrease in MMP and intracellular

ATP, respectively, in a dose-dependent manner. These results suggest that plant-derived aromatic compounds vanillin and vanillic acid may inhibit rotenone-induced neurite shortening and apoptosis-related membrane changes, along with inhibiting ROS accumulation and mitochondrial dysfunction.

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Topic: C.03. Parkinson’s Disease

Title: High-throughput Screening of TMEM175 in their Native Environment.

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Abstract: The lysosome is an essential organelle, participating in clearance and mitophagy. Aberrant lysosome activity can lead to lysosomal storage diseases and disorders of high energy tissue such as Dopaminergic neurons. Now that genetic screening is readily available, over 25% of once idiopathic Parkinson’s Disease has been attributed to the TMEM175 M393T Loss of Function variant. However, traditional whole-cell patch clamp of lysosomes is laborious and extremely specialized. Further, TMEM175 has lysosome specific binding partners, making it a difficult target for pharmacological screens. Sophion Bioscience has therefore continued to expand our Lysosomal Ion Channel profile to include TMEM175 using Oria Bioscience LYSO-Preps™. Using the Qube384 and QPatch48 platforms we have demonstrated the ability to capture lysosomes with a success rate of >70%. We further demonstrate the ability to record concentration-response curves to DCPIB and ionic substitutions.

Disclosures: G. Moody: A. Employment/Salary (full or part-time):; Sophion Bioscience. **E. Waloschková:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **A. Bara:** A. Employment/Salary (full or part-time):; Sophion Bioscience. **B. Masson:** A. Employment/Salary (full or part-time):; Oria Bioscience. **A. Santinho:** A. Employment/Salary (full or part-time):; Oria Bioscience.

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PSTR089: Therapeutic Strategies for Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Title: In vitro PD models for efficacy evaluation of neurotoxicity and dopaminergic neuron degeneration

Authors: J. JIN[1], L. CHEN[1], J. XU[1], S. ZHANG[1], ***P. YE**[1], R. FENG[2];
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Abstract: Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, characterized by motor and non-motor symptoms, which are caused by the degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc). The pathology arises alongside the accumulation of Lewy bodies composed of aggregated α-synuclein(α-syn). Although no model can recapitulate the pathology precisely, the development of PD models is still important and can provide valuable information that can contribute to our understanding of the limitations of the disease and treatment options.We established relevant in vitro models of PD using rodent primary ventral midbrain neurons, human cell lines and hiPSC-derived dopaminergic neurons. First, treatment of primary ventral midbrain neurons with α-syn and Conduritol B epoxide (CBE) significantly reduced cell viability and inhibited dopaminergic axonal outgrowth. Second, we employed LUHMES cells, after differentiating them into dopaminergic neurons and verifying the differentiation efficiency, further applied α-syn and CBE to the LUHMES-derived dopaminergic neurons to establish a PD model and evaluated neuroprotective effects using standard therapeutic agents. Additionally, we also constructed a rotenone-induced model using SH-SY5Y cells to expand the diversity of cell models. Third, we successfully generated and functionally validated hiPSC-derived dopaminergic neurons, demonstrating their capacity to recapitulate biomarker and neuronal network activity. Building on this, we propose a future PD model applying CBE and α-synuclein to these hiPSC-derived dopaminergic neurons, which offers a human-relevant platform for investigating mechanistic studies, screening neuroprotective compounds.Taken together, this work bridges conventional and next-generation in vitro PD models, providing a robust foundation for mechanistic studies and therapeutic development. As our understanding of the disease deepens, an increasing number of underlying mechanisms have been elucidated. We are committed to staying abreast of the latest advancements in the field and will continuously refine our models to provide robust technological platforms for disease research and drug development.

Disclosures: J. Jin: A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **L. Chen:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **J. Xu:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **S. Zhang:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **P. Ye:** A. Employment/Salary (full or part-time):; Shanghai Chempartner Co., Ltd. **R. Feng:** A. Employment/Salary (full or part-time):; ChemPartner Corporation.

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Location: WCC Halls A-C

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Program #/Poster #: PSTR089.09/T22

Topic: C.03. Parkinson's Disease

Title: Intact Neuronal Organelles: A First-In-Class Multimodal Bioreagent For Drug Discovery, Subcellular Omics, Structural Biology, And Neurotoxicity Assessment

Authors: A. SANTINHO[1], B. MASSON[1], **H. GAUTIER**[1], J. LE GALL[1], J. MORCEL[1], L. LEONELLI[1], E. ANDRAOS[1], R. AMEDZROVI AGBESI[1], *H. CARRAT[1], A. THIAM[1,2,3]; [1]ORIA Biosci., Paris, France; [2]ENS PSL, Paris, France; [3]CNRS, Paris, France

Abstract: Lysosomes and mitochondria are convergent hubs in the pathogenesis of neurodegeneration, yet the field has lacked scalable tools to isolate these organelles while preserving membrane integrity, luminal content, and native protein interactions: the precise features that govern drug target biology and enzyme function. Existing methods, including density-gradient ultracentrifugation and immunoprecipitation-based approaches, either compromise organelle integrity or alter surface protein composition, rendering them incompatible with functional or structural assays at very large scales. We describe a proprietary microfluidic platform that extracts intact lysosomes and mitochondria from neuroblastoma cells and iPSC-derived dopaminergic neurons with >90% organelle purity, maintaining functional stability for >1 month. These unique isolated organelles allow a throughput of up to 5,000 data points per day in a screening assay. Leveraging this, we establish the first HTS-compatible plate-reader enzymatic assays performed directly on whole, intact organelles, including GBA1, the most prevalent genetic risk factor for Parkinson's disease, beta-hexosaminidase, and citrate synthase. By eliminating the cellular barrier, these assays reveal true compound potency at the organelle, decoupled from membrane permeability and off-target cellular responses. At this purity and scale, intact organelles unlock three applications previously out of reach: subcellular multi-omics to resolve native enzyme interactomes; direct organelle-level neurotoxicity screening; and detection of lysosomal accumulation and mitochondrial respiratory impairment at sub-cytotoxic concentrations that are invisible to whole-cell assays (Rosell-Hidalgo et al., Biomedicines 2023). Delivered as ready-to-use, plug-and-play preparations, this platform represents a new convergence point for pharmacology, structural biology, omics, and safety in neurodegeneration research.

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Innovative Minds Program grant to Christian Hoffmann

Title: Towards Reverse Engineering of Lewy Body-Like Structures by Phase Separation of Alpha-Synuclein

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Abstract: Alpha-synuclein is an essential protein for the synaptic vesicles cycle, highly enriched in neuronal synapses. However, in disease it accumulates in soma, forming the insoluble inclusions referred to as Lewy bodies (LBs), disrupting neuronal function. Understanding this transformation of soluble α-synuclein into pathological Lewy bodies has been a long-standing challenge with great clinical importance. Current mechanisms and experimental systems are based on treatments of cells and animals with the pre-formed fibrils of α-synuclein, which does not account for the disease onset in humans presumably not exposed to exogenous α-synuclein fibrils. Here, we employed in vitro reconstitutions, theoretical and computational modeling and the minimal in cellulo system to recapitulate the formation of LB-like structures with only two synaptic proteins - α-synuclein and synphilin-1. Specifically, acutely induced increase of synphilin-1 concentration leads to the formation of condensates that enrich α-synuclein, resulting in demixing of these inclusions into core and shell architecture, a stereotypical morphology of LBs. Utilizing live-cell confocal imaging, we found that LB-like inclusions sequester membrane-bound organelles, resulting in the accumulation of fragmented mitochondria at the interface of condensates in the actin-dependent manner. These observations have been validated in post-mortem patient samples: LB-like inclusions reliably recapitulate molecular features of LBs such as phosphorylation pattern of α-synuclein, fragmentation of mitochondria and the upregulation of proteasome degradation signals. Together, our current data reveal that LB-like inclusions arise from the aberrant liquid-liquid phase separation of α-synuclein, which disrupts the intracellular organellar trafficking, providing a new angle for a development of targeted therapies for synucleinopathies.

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Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R21NS140879-01A1

Title: Development and characterization of proSAAS-secreting human iPSC-derived neural progenitor cells for Parkinson's disease

Authors: *V. VINOD[1], Z. SHU[3], H. LAM[4], C. N. SVENDSEN[2], N. T. MAIDMENT[5], A. LAPERLE[6];
[2]Regenerative Med. Inst., [1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]Dept. of Psychiatry and Biobehavioral Sci., UCLA Chapter, Los Angeles, CA; [4]UCLA, Los Angeles, CA; [5]Dept Psychiatry, UCLA Semel Inst., Los Angeles, CA; [6]Cedars-Sinai Regenerative Med. Inst., Los Angeles, CA

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the pathological aggregation of α-synuclein (α-syn) and the loss of dopaminergic neurons in the substantia nigra. Chaperone proteins are emerging as promising therapeutic agents capable of interfering with early α-syn misfolding and aggregation. ProSAAS is a neural secretory chaperone that blocks α-syn fibrillation, attenuates α-syn-induced neurotoxicity in primary dopaminergic cultures, and reduces α-syn-mediated pathology in rodent models of PD. To develop a clinically translatable cell-based delivery platform for proSAAS, we generated a clonal human iPSC line expressing proSAAS under the constitutive PGK promoter. Using established differentiation protocols, engineered iPSCs were differentiated into induced neural progenitor cells (iNPCs) and expanded as free-floating neurospheres. Following differentiation, iNPC identity was confirmed by immunocytochemistry for Nestin, Vimentin and GFAP. Bulk RNA sequencing demonstrated strong concordance between proSAAS-iNPCs and previously characterized GDNF-iNPC populations, indicating that constitutive proSAAS expression does not alter acquisition of the neural progenitor cell state. Production of proSAAS was validated in both the engineered iPSC clones as well as the differentiated iNPCs via immunocytochemistry, western blot, and ELISA. As we had previously observed the development of de novo trisomy of chromosome 12 during the iNPC differentiation and expansion process, we performed G-band karyotyping to assess genomic stability in the differentiated progenitor population. Analysis of conditioned media demonstrated robust secretion of proSAAS, predominantly as the processed 17-kDa form. Ongoing studies are evaluating whether proSAAS-expressing iNPCs can reduce α-syn accumulation and preserve tyrosine hydroxylase-positive neurons in dopaminergic cultures derived from patients with sporadic young-onset PD. Both direct co-culture and conditioned-media paradigms are being used to distinguish cell-contact-dependent and paracrine mechanisms of action. These findings establish a scalable human iPSC-derived platform for sustained delivery of the secreted chaperone proSAAS and support further development of a non-viral cell-based therapeutic strategy for Parkinson's disease.

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Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.12/T25

Topic: C.03. Parkinson's Disease

Title: Modeling α-synuclein neurotoxicity using a human iPSC-derived tri-culture and comparative single-cell RNA-seq analysis of Parkinson's disease brain

Authors: *H. KOBAYASHI, K. NAKATANI, M. UMEKAWA, S. ENDOH-YAMAGAMI; Bio Sci. & Engin. Labs., FUJIFILM Corp., Kanagawa, Japan

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the aggregation of α-synuclein and the progressive loss of dopaminergic neurons in the substantia nigra. In PD, activated microglia induce neuroinflammation, which in turn drives astrocytes from a neuroprotective to a neurotoxic phenotype. In this study, we established a tri-culture system using human iPSC-derived dopaminergic neurons, astrocytes, and microglia, and recapitulated dopaminergic neuronal death following α-synuclein-induced activation of microglia and astrocytes. Furthermore, to examine whether molecular changes observed in this in vitro model reflect those in human PD brains, we performed single-cell RNA-seq analysis and compared gene expression changes with single-cell RNA-seq datasets from PD brains.
To evaluate glia-mediated neurotoxicity, an astrocyte/microglia co-culture was stimulated with α-synuclein preformed fibrils (PFFs) and IFN-γ, followed by the application of dopaminergic neurons, which subsequently showed neuronal damage. α-Synuclein has been reported to activate microglia via Toll-like receptors, leading to downstream nuclear translocation of NF-κB. Consistently, NF-κB localization analysis revealed that α-Synuclein PFF stimulation induced nuclear translocation in both astrocytes and microglia. In addition, treatment with TLR inhibitors partially suppressed NF-κB nuclear translocation and neurotoxicity, suggesting that TLR signaling is involved in α-synuclein PFF-induced neuronal damage.
To further assess whether these changes reflect molecular states observed in PD brains, we performed single-cell RNA-seq analysis on the iPSC-derived tri-culture of dopaminergic neurons, astrocytes, and microglia following stimulation with α-synuclein PFFs and IFN-γ. Transcriptional changes are being analyzed in a cell type-specific manner and compared with public single-cell RNA-seq datasets from PD brains to evaluate disease relevance.
In summary, we induced neurotoxicity associated with microglial and astrocyte activation by α-synuclein PFFs and showed the involvement of TLR signaling. Additionally, through single-cell analysis, we are evaluating whether this model recapitulates cellular states observed in PD brains. This study provides a platform linking human iPSC-based in vitro models with patient brain data, contributing to disease understanding as well as therapeutic and biomarker research.

Disclosures: H. Kobayashi: A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **K. Nakatani:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **M. Umekawa:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation. **S. Endoh-Yamagami:** A. Employment/Salary (full or part-time):; FUJIFILM Corporation.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.13/T26

Topic: C.03. Parkinson's Disease

Title: PON2-dependent autophagy activation by vutiglabridin attenuates α-synuclein pathology in Parkinson's disease models

Authors: *M. LEE[1], J. LEE[3], S. LEE[3], Y. KIM[1], J. CHANG[1,2];
[1]Dept. of Biomed. Sci., [2]Dept. of Brain Sci., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of; [3]Glaceum Inc., Suwon, Korea, Republic of

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the accumulation of misfolded α-synuclein and the loss of dopaminergic neurons. Impaired autophagy, a principal route for the clearance of aggregation-prone proteins, is increasingly recognized as a contributor to α-synuclein pathology, yet current therapies remain symptomatic and do not alter disease progression. Pharmacological activation of autophagy has therefore emerged as an attractive disease-modifying strategy. Vutiglabridin is a small-molecule candidate proposed to activate autophagy, but whether it engages autophagy in neuronal cells, and the mechanism underlying any such effect, had not been defined. In this study, we evaluated whether vutiglabridin activates autophagy in human SH-SY5Y neuroblastoma cells and whether this activity supports its potential as a therapeutic candidate for PD, focusing on the role of paraoxonase 2 (PON2), a neuroprotective enzyme implicated in autophagy regulation. Vutiglabridin promoted autophagy in SH-SY5Y cells and restored the autophagic impairment induced by MPP^+ in a cellular PD model. This recovery was abolished by PON2 knockdown, indicating that the autophagy-activating effect of vutiglabridin is PON2-dependent. Consistent with the in vitro findings, oral administration of vutiglabridin in an α-synuclein A53T mouse model restored brain autophagy markers and selectively reduced α-synuclein oligomers. Collectively, these results indicate that vutiglabridin activates autophagy through a PON2-dependent mechanism and thereby attenuates α-synuclein oligomer accumulation in both in vitro and in vivo PD models. Beyond identifying vutiglabridin as a candidate worthy of further development, this work highlights the PON2-autophagy axis as a previously underexplored and potentially druggable target, providing a mechanistic rationale for evaluating PON2-acting autophagy activators as disease-modifying approaches to Parkinson's disease.

Disclosures: M. Lee: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Glaceum Inc. **J. Lee:** A. Employment/Salary (full or part-time):; Glaceum Inc. **S. Lee:** A. Employment/Salary (full or part-time):; Glaceum Inc. **Y. Kim:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Glaceum Inc. **J. Chang:** 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.; Glaceum Inc.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Glaceum Inc..

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.14/T27

Topic: C.03. Parkinson's Disease

Support: Advanced Research and Invention Agency (ARIA) SCNI-PR01-P014

Title: Engineering human dopaminergic microtissues with A9-associated phenotype for pathway reconstruction in Parkinson's disease

Authors: *D. BOUFIDIS[1], D. CHOUHAN[2], V. ALPIZAR VARGAS[1], S. KARANDIKAR[1], F. VITALE[3], D. CULLEN[4];
[1]Univ. of Pennsylvania, Philadelphia, PA; [2]Dept of Neurosurg., Univ. of Pennsylvania, Cherry Hill, NJ; [3]Univ. of Pennsylvania, Philadelipha, PA; [4]Neurosurg., Univ. of Pennsylvania, Media, PA

Abstract: Parkinson's disease (PD) graft strategies aim to restore dopaminergic signaling, but grafts must do more than survive: they should acquire the appropriate midbrain phenotype to enable preferential axonal integration with striatal targets as in the lost nigrostriatal pathway. Because the A9 sub-phenotype of dopaminergic neurons is preferentially lost in PD and innervates the dorsal striatum, advanced graft strategies should move beyond reliance on tyrosine hydroxylase (TH) expression alone - the standard marker of pan-dopaminergic neurons - to resolve A9/A10-associated identity, maturation, and spatial organization. We developed an anatomically inspired human dopaminergic microtissue platform to evaluate these design criteria. Human iPSC-derived dopaminergic neurons from two sources were compared in 2D culture, 3D aggregates, and hydrogel-confined microtissues using phase imaging and immunocytochemistry. In 2D and 3D culture, the higher-TH cell source showed greater dopaminergic purity, whereas the A9-enriched cell source showed greater GIRK2 enrichment and lower calbindin presence. In hydrogel-confined microtissues, both sources showed progressive axonal growth, full-column axonal tracts by 21 days *in vitro* (DIV), and bundled TH^+ axons at 48 DIV. Also, TH expression in neuronal aggregates increased from 14 DIV to 28 DIV, suggesting ongoing neuronal maturation and neuritic arborization. To determine whether mature grafts organized into phenotype-relevant compartments, 8-week microtissues were segmented into peripheral, middle, and core regions. TH^+ neuronal somata were abundant in the peripheral compartment, while dense regions showed higher nuclear density and lower TH^+ expression. Across matched mature samples, TH^+ territory overlapped more strongly with GIRK2 than calbindin, supporting an A9-associated phenotype. In striatal co-cultures, dopaminergic axons interfaced with human medium spiny neuron aggregates, with TH^+ processes and Synapsin 1 signal detected within $DARPP32^+$ target regions. Together, these findings establish a spatially organized A9-enriched dopaminergic microtissue featuring long-projecting axonal tracts and capacity for synaptic integration with striatal neurons that may be suitable as a graft substrate to treat PD.

Disclosures: D. Boufidis: None. **D. Chouhan:** None. **V. Alpizar Vargas:** None. **S. Karandikar:** None. **F. Vitale:** None. **D. Cullen:** None.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.15/T28

Topic: C.03. Parkinson's Disease

Support: Advanced Research and Invention Agency (ARIA) SCNI-PR01-P014

Title: Comparing optical and electrical stimulation of bioengineered dopaminergic tissue using fast-scanning cyclic voltammetry and chemometric analysis

Authors: *A. J. WEISSMAN[1,2], D. CHOUHAN[2], S. R. COHEN[5], K. YANKSON[3], V. ALPIZAR VARGAS[3], D. BOUFIDIS[4], S. KARANDIKAR[3], F. VITALE[3], R. A. ESPAÑA[6], D. CULLEN[2];
[1]Univ. of Pennsylvania, Oreland, PA; [2]Neurosurg., [4]Bioengineering, [3]Univ. of Pennsylvania, Philadelphia, PA; [6]Neurobio. and Anat., [5]Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Parkinson's disease results from degeneration of the nigrostriatal pathway, reducing dopamine signaling in the striatum. To reestablish dopamine levels in the striatum, we are developing a three-dimensional (3D) bioengineered dopaminergic microtissue to provide an alternative source of dopamine to striatal circuitry. With optogenetically responsive dopaminergic neurons, this bioengineered microtissue allows dopamine release to be precisely controlled with light, potentially offering a biologically-based alternative to deep brain stimulation. In this study, we used fast-scan cyclic voltammetry (FSCV) to measure evoked dopamine release from the bioengineered dopaminergic microtissue comprising a distinct aggregated population of neurons and long-projecting axonal tracts within the lumen of a hydrogel microcolumn. During biofabrication, human iPSC-derived dopaminergic neurons were transduced using adeno-associated virus (AAV) to express ChrimsonR, ChRmine, or Channelrhodopsin. Over weeks *in vitro*, these transduced neurons survived and extended long axonal tracts - at levels equivalent to non-transduced controls - and gradually increased fluorescent reporter expression (a surrogate for opsin expression) over time. After maturation, these microtissues were stimulated optically at wavelengths matched to each opsin, with electrical stimulation used as an opsin-independent reference condition. To keep the comparison focused on stimulation type and opsin identity, the stimulation pattern was held constant across conditions. Carbon-fiber microelectrodes were placed near the dopaminergic aggregate region to measure local dopamine signals. Because of this electrode placement, the measured signals resembled dopamine release patterns reported in the substantia nigra rather than the typical axon-terminal release in the striatum. Principal component regression chemometrics were used to separate dopamine from background drift, pH changes, and stimulation-related artifacts. To date, optically-evoked release has only resulted in peak local dopamine concentrations of 75-80 nM - approximately 10% of that achieved with electrical stimulation at matched time points - which may be optimized based on improving transduction efficiency, stimulation parameters, and/or microtissue maturation. Ongoing analyses will also determine whether the magnitude or features

of the evoked response vary by opsin identity or stimulation modality. This novel optogenetically-active 3D dopaminergic microtissue may serve as a component of an implantable closed-loop system for controlled replenishment of dopamine levels in Parkinson's disease.

Disclosures: A.J. Weissman: None. **D. Chouhan:** None. **S.R. Cohen:** None. **K. Yankson:** None. **V. Alpizar Vargas:** None. **D. Boufidis:** None. **S. Karandikar:** None. **F. Vitale:** None. **R.A. España:** None. **D. Cullen:** None.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.16/T29

Topic: C.03. Parkinson's Disease

Support: Advanced Research and Invention Agency (ARIA) SCNI-PR01-P014

Title: Development and Characterization of Optogenetically-driven Dopaminergic Tissue-engineered Living Electrodes for Closed-Loop Neuromodulation in Parkinson's Disease

Authors: *D. CHOUHAN[1], K. YANKSON[2], A. WEISSMAN[1], V. ALPIZAR VARGAS[2], S. KARANDIKAR[2], D. BOUFIDIS[2], K. D. BROWNE[1], F. VITALE[3], D. CULLEN[4]; [1]Neurosurg., [2]Bioengineering, [3]Bioengineering and Neurol., [4]Neurosurg. and Bioengineering, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Nigrostriatal pathway degeneration in Parkinson's disease (PD) causes severe depletion of the neurotransmitter dopamine within the striatum. As such, neuromodulation techniques such as deep brain stimulation have emerged to manage the resulting motor symptoms. However, neuromodulation strategies for PD require high spatial and cellular specificity to restore lost neurochemical connectivity without off-target effects. To address this, we have developed dopaminergic tissue engineered living electrodes (dTELEs) using a combination of stem cell, biomaterial, viral-transduction, and controlled bioassembly techniques. Utilizing soft and biocompatible materials acting as a hydrogel microcolumnar scaffold, we have developed a microtissue comprising channelrhodopsin-transduced human iPSC-derived dopaminergic neurons and long-spanning, bundled axonal tracts. The dTELEs feature implantable dimensions of hundreds of microns in diameter with millimeter-to-centimeter lengths of pre-grown axonal tracts to accommodate deep targets in the brain. Importantly, we have shown that dTELE activity can be controlled by external light stimulus, thereby offering a highly targeted, biohybrid alternative to conventional stimulating electrodes. Axonal outgrowth within the dTELEs reached 5 mm by 10 days *in vitro* (DIV), 10 mm by DIV18, and over 20 mm by DIV49. Immunohistochemistry (IHC) results confirmed the microtissue is highly enriched for the A9 dopaminergic neuron subtype, the primary population responsible for striatal innervation. Optogenetic capabilities and health of the living electrodes were independently validated for

expression of three distinct opsins, namely, ChRmine (~585 nm) and ChrimsonR (~590 nm) for red light, and ChR2 (~470 nm) for blue light excitation. Optically-evoked dopamine release from the engineered microtissue confirmed functional activity *in vitro*. Further, to model targeted striatal innervation *in vitro*, human striatal medium spiny neurons (MSNs) were seeded at the opposite end to connect with the long-projecting dopaminergic axon tracts. Live cell imaging showed robust ChR2+ axon outgrowth arborizing and innervating the MSNs. IHC revealed dopaminergic synaptic markers between long dopaminergic axons and local MSN somata and dendrites, suggesting appropriate synaptic integration. Ongoing studies are focused on integrating the dTELEs with a custom micro-LED and a miniaturized biosensor to yield a dynamic closed-loop system capable of recording striatal dopamine levels in real time and controlling optogenetic stimulation, thereby offering a precise synaptic-based neuromodulation therapy for PD.

Disclosures: D. Chouhan: None. **K. Yankson:** None. **A. Weissman:** None. **V. Alpizar Vargas:** None. **S. Karandikar:** None. **D. Boufidis:** None. **K.D. Browne:** None. **F. Vitale:** None. **D. Cullen:** None.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.17/T30

Topic: C.03. Parkinson’s Disease

Title: Drastically Accelerated Manufacture of Human Induced Pluripotent Stem Cell-Derived Midbrain Dopaminergic Neurons for Drug Discovery and Cell Replacement Therapy

Authors: *P. WALSH, T. KNOX, V. TRUONG;
Anatomic Inc., Minneapolis, MN

Abstract: Parkinson’s Disease (PD) results from the loss of dopaminergic neurons (DANs) of the substantia nigra pars compacta that causes both motor and non-motor symptoms. Typical motor symptoms of PD include resting tremors, muscle stiffness, slowness of movement, and impaired balance; while non-motor symptoms include loss of smell, sleep disturbance and mood changes. Over 10 million are living with PD currently, with 90,000 new diagnoses every year. New methods to prevent or treat PD are in need. One promising approach for both disease modeling and cell replacement therapy includes the differentiation of human pluripotent stem cell (hPSC)- derived DANs. Despite enormous investment, manufacture of these cells remain a challenge. Differentiation protocols for disease modeling span greater than 40 days with resulting populations producing at most 15% DANs. These differentiation protocols are adapted for cell replacement therapy by dissociating and transplanting in vivo day 20 floorplate progenitors, which is risky given these cells do not uniformly differentiate into DANs in vitro. Substantial additional progress needs to be made in the efficient and scalable manufacture of hPSC-derived DANs focusing on both speed and purity. Here we report a novel, accelerated

method to differentiate hPSC-derived midbrain floorplate DANs. This method is morphogen-guided, following embryological principles to create expected developmental landmarks resulting in high-purity DANs. Within the span of only 7 days, hPSCs can be differentiated into OTX2/PAX2/EN1/FOXA2-expressing midbrain floorplate cells and terminally differentiated into immature FOXA2/TUJ1 midbrain DANs. These terminally differentiated immature cells can be further matured for assay development over the course of several weeks. Immunocytochemically, DANs maintain expression of FOXA2 and TUJ1, and gain expression of tyrosine hydroxylase. qPCR demonstrates expression of key DAN genes such as FOXA2, PITX2, and TH. Transcriptomics of the current method is compared against currently established methods and in vivo midbrain tissue looking at principle component analysis and key gene expression levels. Functionally, these DANs gradually evolve spontaneous action potential firing on multielectrode array. This method produces highly enriched midbrain DANs in a very short time, allowing for easier downstream assay development. Because this method relies exclusively on a 7-day, simplified differentiation kit containing chemically defined reagents amenable to manufacture using current good manufacturing practices, this protocol is highly amenable to cell replacement therapy.

Disclosures: P. Walsh: A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **T. Knox:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. **V. Truong:** A. Employment/Salary (full or part-time):; Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR089: Therapeutic Strategies for Parkinson's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR089.18/T31

Topic: C.03. Parkinson’s Disease

Support: National Institutes of Health Grant R01-NS117757
National Institutes of Health Grant R01-NS127895

Title: Assessing long-term dopamine output and target innervation in human iPSC-derived tissue engineered nigrostriatal pathways

Authors: *S. P. KARANDIKAR[1], D. CHOUHAN[2], K. D. BROWNE[2], J. E. DUDA[3], D. CULLEN[2];
[1]Bioengineering, [2]Dept. of Neurosurg., [3]Dept. of Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Parkinson's Disease drives >30% loss of dopaminergic neurons within the Substantia Nigra pars compacta and concomitant ~50% reduction in Striatal dopamine by the time of clinical presentation, driving devastating motor dysfunction and >$50B USD in direct and indirect annual costs in the U.S. alone. Our group has developed Tissue Engineered Nigrostriatal Pathways (TE-NSPs), which are implantable columnar hydrogels bearing a controlled number of human induced-pluripotent stem cell (iPSC) derived dopaminergic neurons with long-projecting axonal tracts spanning several millimeters for proof-of-concept testing in rats and several centimeters to demonstrate feasibility of human-scale grafts. By reconstituting the nigrostriatal pathway upon stereotactic delivery, TE-NSPs pre-grown *in vitro* inherently obviate the need for long-distance, targeted axonal outgrowth *in vivo* typically required for homotopic cell replacement therapies, yielding a straightforward future clinical paradigm. Through tissue clearing and fast scan cyclic voltammetry (FSCV), we demonstrated TE-NSP survival and dopamine release both *in vitro* and after transplantation in 6-OHDA hemi-lesioned rodents up to 6 months post-implant. In particular, at 35 days post-assembly, *in vitro* intra-tract FSCV yielded dopamine concentrations of 90.8 +/- 27.9 nM (3,300 neurons), and 495.4 +/-127.6 nM (100,000 neurons), respectively. At 3 months post transplantation, we further observed intra-striatal dopamine release of 135.5 +/- 9.2 nM in TE-NSP implanted subjects, as opposed to 62.0 +/- 21.5 nM in acellular hydrogel implanted controls. Furthermore, axonal egress from TE-NSPs was visualized at 3 and 6 months post-transplantation, revealing statistically significant but modest outgrowth of Tyrosine Hydroxylase (TH) and human Neural Cell Adhesion Marker (hNCAM) positive, transplant-derived axons in the host striatum. To improve on the rate and extent of striatal axonal arborization from TE-NSPs, we overexpressed Glial Cell-line Derived Neurotrophic Factor (GDNF) in iPSC-derived dopaminergic neurons as well as in striatal end target neurons via adeno-associated viruses and compared the performance of each modification individually in accelerating intra-lumen axonal outgrowth after fabrication of TE-NSPs. This work confirms the viability of TE-NSP transplantation and sets the stage for future chemotactic integration and long-term behavioral efficacy studies. As such, it establishes significant foundational evidence in support of human iPSC-derived TE-NSPs as a potential restorative microtissue therapy paradigm for the treatment of PD related motor symptoms.

Disclosures: S.P. Karandikar: None. **D. Chouhan:** None. **K.D. Browne:** None. **J.E. Duda:** None. **D. Cullen:** None.

Poster

PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.01/T32

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 NS117469

Title: The neural mechanisms underlying the ameliorating effect of resveratrol on vocalization deficits in Parkinsonian Pink1-/- rats

Authors: *C. ZHAO, S. A. LECHNER, C. A. KELM-NELSON;
Dept. of Surgery, Div. of Endocrine Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Parkinson disease (PD) is a progressive neurodegenerative disease primarily characterized by motor dysfunction. Because disease-modifying treatments for PD remain limited, identifying early pathological changes and gene expression signatures is critical for developing effective therapeutic strategies. The *Pink1-/-* rat is a well-established model of prodromal PD that replicates the early-stage motor and vocalization deficits in humans with PD. Previous work from our laboratory has demonstrated that systemic administration of resveratrol, a compound with anti-inflammatory, antioxidant, and anti-apoptotic properties, ameliorates vocalization deficits and reduces whole blood inflammation-related transcription profiles in *Pink1-/-* rats. However, the neural mechanisms underlying these beneficial effects remain unclear. SNAP-25 is a presynaptic membrane protein that plays a critical role in neurotransmitter release, synaptic plasticity, neurite outgrowth, and neuronal development. Alterations in SNAP-25 expression or function have been associated with PD. Therefore, the present study investigated whether the improvement in vocalization with systemic resveratrol in *Pink1*-/- rats occurs through the modulation of SNAP-25 mRNA expression in the periaqueductal gray (PAG), a brain region involved in vocal production. Two groups of male *Pink1-/-* rats at 4 and 10 months of age were randomly assigned to receive either vehicle (saline; $n = 10$) or resveratrol (20 mg/kg; $n = 10$). Animals received the assigned treatment daily in a 4-g sugar cookie for 8 consecutive weeks. Vocalization testing was conducted at baseline and after drug treatment for all rats. Following the treatment period, SNAP-25 mRNA expression in the PAG was analyzed using RNAscope in situ hybridization. There were no interactions between timepoint and treatment for any vocalization variables at 4 months of age. In contrast, resveratrol significantly improved vocalization outcomes including peak frequency, at 10 months of age. Additionally, resveratrol significantly increased SNAP-25 mRNA expression in the PAG at both 4 and 10 months of age. Given that reduced SNAP-25 expression has been linked to limb motor deficits in PD, these findings suggest that resveratrol may ameliorate vocal motor impairments in PD, at least in part, by enhancing SNAP-25 expression in the PAG.

Disclosures: C. Zhao: None. **S.A. Lechner:** None. **C.A. Kelm-Nelson:** None.

Poster

PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.02/U1

Topic:

Support: NIH 2R01NS117469

Title: Adalimumab, a TNF-α inhibitor, improves vocal communication deficits in male Pink1-/- rats

Authors: *S. A. LECHNER[1], C. ZHAO[2], C. A. KELM-NELSON[2];
[1]Dept. of Surgery | Div. of Endocrine Surgery, Univ. of Wisconsin, Madison, Madison, WI;
[2]Dept. of Surgery | Div. of Endocrine Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Nearly 90% of individuals with Parkinson disease (PD) develop early-onset vocal deficits that do not respond effectively to current pharmacological treatments. Our lab uses a well-validated rat model of PD with a homozygous knockout of *Pink1* (PTEN-induced putative kinase 1) that demonstrates early and age-progressive vocal deficits, limb motor deficits, and preclinical neural pathologies analogous to humans with PD. In humans, loss of PINK1 protein causes an increase in numerous pro-inflammatory markers including tumor necrosis factor-alpha (TNF-α) and nuclear factor-kappa B (NF-kB). We have shown that male *Pink1-/-* rats demonstrate upregulated gene expression of TNF-α in the thyroarytenoid muscle, a vocal fold muscle crucial to proper vocal production. Therefore, we hypothesized that Adalimumab (Humira®), a TNF-α blocker, would reduce peripheral- and neural-inflammation and subsequently improve vocalization deficits and reduce brainstem inflammation. This study was performed on two separate groups of male *Pink1-/-* rats at 12 months of age [(vehicle ($n = 8$); adalimumab ($n = 8$)]. All rats received either an induction dose of adalimumab (10mg/kg) or saline vehicle control administered intraperitoneally followed by a 'maintenance' dose (5mg/kg) on day 15, similar to what is standard administration protocol in humans. Ultrasonic vocalizations and limb motor function were assessed at baseline, prior to the first injection, and at least 14 days after the second injection. Paired *t*-tests were used to determine statistically significant differences between acoustic and non-acoustic parameters of call types and limb motor behaviors. Critical level of significance was set *a priori* at 0.05. Results demonstrated that adalimumab significantly increased intensity, bandwidth, and peak frequency of USVs in male *Pink1-/-* rats. Analysis is currently ongoing for the vehicle control group as well as immunolabeling for TNF-α to investigate effects of adalimumab in the vocal motor regions of the brainstem. Immunolabeling will be correlated to behavioral outcomes in both groups. This is the first study to suggest that multiple acoustic parameters of *Pink1-/-* rat USVs can be modified by TNF-α blockers such as adalimumab.

Disclosures: S.A. Lechner: None. **C. Zhao:** None. **C.A. Kelm-Nelson:** None.

Poster

PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.03/U2

Topic: C.03. Parkinson's Disease

Title: A Searchable, Curated Database Reveals Reproducible Gut Microbiome Signatures in Parkinson's Disease

Authors: *D. SLOCUM;
Sci. and Technol., Endicott Col., Marblehead, MA

Abstract: Title: A Searchable, Curated Database Reveals Reproducible Gut Microbiome Signatures inParkinson's Disease**Abstract:**Alterations in the gut microbiome have been increasingly implicated in Parkinson's disease(PD), yet findings across studies remain variable and difficult to integrate. To address thischallenge, I developed a structured, searchable database integrating microbiome–PD associationsfrom 30 peer-reviewed studies. Taxonomic, clinical, and methodological variables werestandardized into a unified schema, and a replication metric was introduced to quantify theconsistency of microbial associations across studies.The resulting dataset includes over 100 taxon-level associations spanning 30 studies and 37unique taxa. Cross-study analysis identified a subset of reproducible microbial signatures,including depletion of short-chain fatty acid–producing taxa such as *Faecalibacterium*,*Roseburia*, and *Prevotella*, and enrichment of taxa associated with inflammation and mucindegradation, including *Akkermansia*, *Lactobacillus*, and members of the *Enterobacteriaceae*family. These patterns were frequently linked to gastrointestinal symptoms such as constipation,supporting the role of the gut–brain axis in PD pathophysiology.An interactive Shiny-based application was developed to enable dynamic filtering bydemographic, environmental, and clinical variables, facilitating cross-study exploration ofmicrobiome patterns. This work provides a scalable framework for integrating microbiomeresearch in PD and highlights reproducible microbial signatures that may serve as potentialbiomarkers or therapeutic targets.

Disclosures: D. Slocum: None.

Poster

PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.04/U3

Topic: C.03. Parkinson's Disease

Support: KIMST Grant RS-2026-25508103

Title: Nurr1-Mediated Suppression of Cellular Senescence Reduces Neuroinflammation in the Aged Brain

Authors: *Y. KIM[1], K. S. KIM[2];
[1]Ajou university, Suwon, Korea, Republic of; [2]Molec Neurobiol Lab., McLean Hospital/Harvard Med. Sch., Belmont, MA

Abstract: Aging is associated with chronic neuroinflammation and the accumulation of senescent cells in the brain. Nurr1 (NR4A2) is a transcription factor essential for dopaminergic neuron maintenance and regulation of inflammatory responses. However, its role in age-associated cellular senescence remains incompletely understood.We investigated whether modulation of Nurr1 signaling influences senescence and neuroinflammation in aged mice. Brain tissues from aged animals treated with a Nurr1-modulating intervention were analyzed for senescence and inflammatory markers using molecular and histological approaches.Nurr1

expression was significantly increased following treatment. This increase was associated with reduced expression of the senescence marker p21 and decreased levels of pro-inflammatory mediators. These findings suggest that Nurr1 activation attenuates senescence-associated inflammatory responses in the aged brain.Our results support a role for Nurr1 in regulating cellular senescence and neuroinflammation during aging and suggest that Nurr1-targeted interventions may represent a therapeutic strategy for age-related neurodegenerative disorders.

Disclosures: Y. Kim: None. **K.S. Kim:** None.

Poster

PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.05/U4

Topic:

Support: NIH grant R01NS119208
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Title: Neurovascular Abnormalities in a G2019S-LRRK2 Mouse Model of Parkinson’s Disease

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Abstract: Neurovascular Abnormalities in a G2019S-LRRK2 Mouse Model of Parkinson's Disease.
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Affiliations[1] Department of Psychiatry and Behavioral Sciences[2] Departments of Biomedical Engineering and Radiology[3] Functional Brain Imaging, Kennedy Krieger Institute
Abstract: Parkinson’s disease (PD) is a common neurodegenerative disease characterized by motor impairments resulting from midbrain dopamine (DA) neuron loss. Mutations in LRRK2 cause genetic PD and contribute to sporadic PD. Here, we used a G2019S-LRRK2-transgenic mouse model to investigate abnormalities in arteriolar cerebral blood volume (CBVa) and lymphatic vessels in various brain regions using inflow-based vascular-space-occupancy (iVASO) and gadolinium-based MRI techniques. CBVa-measured brain regions included the substantia nigra (SN, the PD-affected area), olfactory cortex, and prefrontal cortex. Alterations in the blood volume of small arteries and arterioles (CBVa) were detected in the G2019S-LRRK2 mouse model of PD. Compared to non-transgenic mice, G2019S-LRRK2 mice at the preclinical clinical stage showed increased CBVa, and at the clinical stage showed decreased CBVa in the SN in both male and female groups. In contrast, WT-LRRK2 mice showed no change in CBVa

in the SN (male and female). Moreover, the G2019S-LRRK2 also induced abnormal dynamic signal changes of lymphatic vessels in the basal region (BR) compared with non-transgenic mice at both preclinical and clinical stages. These MRI changes in G2019S-LRRK2 mice were validated by pathological studies and corresponded with PD pathology. Our results suggest the brain MRI changes of CBVa and lymphatic vessels may be useful as a marker for PD disease progression.

Disclosures: S. Zhou: None. **W. Smith:** None. **B. Ning:** None. **J. Hua:** None. **M. Jiang:** None. **C.A. Ross:** None.

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PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

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Program #/Poster #: PSTR090.06/U5

Topic: C.03. Parkinson’s Disease

Support: National Natural Science Foundation of China under grant numbers 32230049, 32341006, and 32400785

Title: Inhibition of astrocytic GFRAL ameliorates disease progression of PD

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Abstract: Inhibition of astrocytic GFRAL ameliorates disease progression in an animal model of Parkinson’s disease Ying Long[1], Jia-wei Zhou [1,*1]*Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology,Chinese Academy of Sciences, Shanghai, 200031, China.**Corresponding authorEmail: jwzhou@ion.ac.cn**Abstract: Objective** Parkinson's disease (PD), a neurodegenerative disorder, is characterized bythe deposition of aggregated alpha-synuclein and the death of nigral dopaminergic neurons. So far,there is still a lack of a disease-modifying treatment. By virtue of their pro-survival activities,neurotrophic factors (NTFs) have emerged as promising candidates to counteract and potentiallyneurodegeneration in PD. However, clinical trials targeting NTFs, such as glial-cell-line-derivedneurotrophic factor have largely been unsuccessful, necessating further exploration into theirtherapeutically potential in PD. Growth differentiation factor 15 (GDF15) is a novel neurotrophicfactor for midbrain dopaminergic neurons in vivo. However, the contribution of the GDF15 andit’s receptor GDNF family receptor alpha-like (GFRAL) to PD pathogenesis remains elusive.Furthermore, astrocytes play essential roles in the maintenance of central nervous systemhomeostasis and contribute to the pathogenesis of neurodegeneration diseases, but previousresearch has primarily focused on the effects of NTFs on neurons, their impact on astrocytesremains largely unexplored. **Methods** The motor ability of A30P mutant α-synuclein transgenicmice was evaluated by using Rotarod, pole test and open field test. The aggregation of α-synucleinwas identified by western blotting. The activation of astrocytes and microglia was

determined bywestern blotting and immunofluorescent staining. **Results** (1) Activation of astrocytic GFRALpromoted disease progression in A30P mice. Selective ablation of GFRAL in astrocytes improvedmotor ability of A30P mice and reduced α-synuclein aggregation. (2) The reduction in glial cellactivation and the decrease in inflammatory pathways, suggesting that GFRAL knockout inastrocytes may alleviate disease progression in A30P mice by suppressing inflammation.**Conclusion** Activation of astrocytic GFRAL contributes to the disease progression in an animalmodel of PD.**Keywords:** Parkinson's disease; GDNF family receptor alpha-like; Astrocyte

Disclosures: Y. Long: None.

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PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

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Program #/Poster #: PSTR090.07/U6

Topic: C.03. Parkinson’s Disease

Support: 2R01ES024745
5R01ES033462

Title: Characterization of genes dysregulated in Parkinson’s disease monocytes

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Abstract: Parkinson’s disease (PD) is a progressive, age-related neurodegenerative disorder characterized by both motor and non-motor manifestations. Increasing evidence implicates peripheral immune dysregulation in PD pathogenesis, highlighting circulating immune cells as a source of disease-relevant biomarkers and therapeutic targets. We previously applied single-cell RNA sequencing to profile peripheral blood mononuclear cells (PBMCs) from PD patients and healthy controls. In the present study, we focus on transcriptional alterations within myeloid subsets to identify novel immune modulators associated with PD. Analysis of $CD14^+$ and $CD16^+$ monocyte populations revealed robust gene expression changes associated with PD. Subsequent prioritization identified a subset of differentially expressed transcripts enriched specifically within myeloid lineages, suggesting cell-type-restricted mechanistic contributions to disease-associated immune phenotypes. Ongoing functional studies examine the response of these candidate genes to oxidative and proteotoxic stress, with emphasis on NLRP3 inflammasome activation, inflammatory mediator release, and mechanisms of neuroinvasion. Parallel translational analyses integrate structural modeling to evaluate interactions between prioritized targets and lead small molecules, supporting the identification of candidate therapeutic compounds. Collectively, these findings advance current understanding of peripheral immune

involvement in PD and establish a framework linking single-cell transcriptomic discovery to functional validation and drug development targeting myeloid-driven mechanisms in neurodegeneration.

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PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR090.08/U7

Topic: C.03. Parkinson’s Disease

Title: Examining the role of neuroinflammation in the spread of alpha-synuclein pathology in a Parkinson's disease mouse model

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Abstract: Examining the role of neuroinflammation in the spread of alpha-synuclein pathology in a Parkinson’s disease mouse model
Alyssa Moskites[1], Sarah Kushner[1], Yee Fun Lee[1], Lauren Norwood[1], Rui Chang[1], Olga Morozova[1], Nadine Ruderisch[1], Jan Stoehr[1], and Tammy Dellovade[1]
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Parkinson’s disease (PD) is an age-related neurodegenerative disorder characterized by alpha-synuclein (α-syn) aggregation and dopaminergic neuron loss in the substantia nigra. This process is accompanied by neuroinflammation, but it is unknown if neuroinflammatory processes modulate disease onset or progression. Therefore, it is unknown if pharmacological modulation of neuroinflammatory processes have the potential as a disease modifying approach in PD.
To investigate these processes in the context of propagation of α-syn pathology we used the M83 mouse model, which overexpresses full length human A53T variant α-syn under the mouse prion promoter. To avoid inducing neuroinflammation by direct intracranial injection, recombinant human pre-formed α-syn fibrils (hPFFs) were injected intramuscularly into the femoris muscle. This model shows propagation of α-syn pathology from the periphery to the CNS, resulting in robust time dependent increases in pathological α-syn species (pS129) and inflammatory markers in the brainstem, midbrain, and hypothalamus of injected mice.
Previous pilot studies have shown that dosing M83 mice with PLX-3397, a CSF1R inhibitor, for seven days significantly reduces Iba1 immunoreactivity in the brainstem, midbrain, and hypothalamus of M83 mice. To assess the contribution of neuroinflammation to the development and spread of α-syn pathology, M83 mice that had received an intramuscular hPFF injection then received set amounts of chow with PLX-3397 or a control chow for four months. After four

months, the brains of injected mice were processed for immunohistochemical analysis of pS129 and markers of glial activation to assess the effect of glial cell depletion within this model.

Disclosures: A. Moskites: A. Employment/Salary (full or part-time):; AbbVie. **N. Ruderisch:** A. Employment/Salary (full or part-time):; AbbVie. **Y. Lee:** A. Employment/Salary (full or part-time):; AbbVie. **L. Norwood:** A. Employment/Salary (full or part-time):; AbbVie. **R. Chang:** A. Employment/Salary (full or part-time):; AbbVie. **O. Morozova:** A. Employment/Salary (full or part-time):; AbbVie. **J. Stoehr:** A. Employment/Salary (full or part-time):; AbbVie. **T. Dellovade:** A. Employment/Salary (full or part-time):; AbbVie. **S. Kushner:** A. Employment/Salary (full or part-time):; AbbVie.

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PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

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Program #/Poster #: PSTR090.09/U8

Topic: C.03. Parkinson’s Disease

Support: MSU TETRAD
Brophy Endowment

Title: Spatial Transcriptomic Analysis of Inflammatory Microglia-T cell Niches Associated with Alpha-synuclein Pathology

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Abstract: Parkinson's disease (PD) is characterized by alpha-synuclein (α-syn) aggregation, neuroinflammation, and progressive degeneration of substantia nigra pars compacta (SNpc) dopaminergic neurons. Both activated microglia and infiltrating T cells are associated with α-syn pathology, however, the functional phenotype of microglia and T cells surrounding aggregate-bearing neurons remains poorly defined. We utilized Multiplexed Error Robust Fluorescence In Situ Hybridization (MERFISH) spatial transcriptomics to investigate transcript expression within inflammatory niches associated with α-syn pathology in the rat preformed fibril (PFF) model of PD. A custom gene panel was designed based on previous RNA sequencing results identifying inflammation-associated transcripts enriched in the SNpc during peak α-syn aggregation. Spatial mapping revealed distinct clusters of microglia and T lymphocytes within the inclusion bearing SNpc. These microglial-T cell niches exhibited abundant expression of genes involved in essential roles in innate immunity, type 1 and type 2 interferon signaling, T-cell activation, antiviral defense and extravasation including Cxcl17, Ifi27l2b, Ifng, Kcnn4, Itgb2, Rtp4 and Rhbdf2. Z-DNA binding protein 1 (Zbp1), a nucleic acid sensor previously implicated in driving type I interferon signaling, also was observed to be upregulated in the microglial-T cell inflammatory niches. Additional analyses will focus on determining whether gene expression changes in microglia, astrocytes and T cells is dependent upon distance to phosphorylated α-syn

inclusions. Ongoing studies utilizing ZBP1 knockout rats will investigate whether ZBP1 contributes to the formation of microglial-T cell inflammatory niches and/or aggregate-associated neurodegeneration. These findings support a model in which α-syn aggregates promote the formation of spatially organized inflammatory microenvironments containing interacting microglial and T-cell populations.

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PSTR090: Parkinson's Disease: Glias and Immune Actions

Location: WCC Halls A-C

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Program #/Poster #: PSTR090.10/U9

Topic: C.03. Parkinson's Disease

Support: This work was funded by the Michael J. Fox Foundation.

Title: PTBP1 Gene Therapy Does Not Convert Astrocytes to Neurons Nor Regenerate Nigrostriatal Dopamine in a Macaque Model of Parkinson's Disease

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Abstract: Suppression of polypyrimidine tract-binding protein 1 (PTBP1) has been proposed to promote astrocyte to neuronal reprogramming and nigrostriatal dopaminergic repair in rodent Parkinsonian models, but its efficacy in primates remains unclear. We tested whether adeno-associated virus (AAV)-delivered short hairpin RNA targeting PTBP1 (AAV-shPTB) converts astrocytes to neurons and improves nigrostriatal dopamine function in a hemiparkinsonian model in cynomolgus macaques. Eight macaques received unilateral 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) through the right carotid artery, producing contralateral motor impairment, and were then randomly assigned to AAV-shPTB (n=4) or luciferase control vector (AAV-shLuc; n=4). Dopaminergic function was measured longitudinally by [18F]-fluorodopa ([18F]-FDOPA) positron emission tomography (PET), with striatal uptake asymmetry calculated as (right-left)/left at post-MPTP baseline, 6 months, and 12 months. Fine motor performance was measured monthly using a hand-reach task requiring bilateral retrieval of six food rewards from a 2 x 3 well matrix. PET imaging confirmed persistent unilateral dopaminergic deficits after MPTP in both groups. Repeated-measures analysis detected no significant effect of treatment ($p=0.8550$), time ($p=0.1909$), or treatment-by-time interaction ($p=0.5913$) on striatal uptake asymmetry. Subject-to-subject variability accounted for most PET variance (88.2%, $p<0.0001$). Behaviorally, left-hand retrieval times were longer than right-hand times, consistent with impairment contralateral to the lesioned hemisphere. AAV-shPTB-treated animals showed lower affected-hand retrieval times than controls across the study; however, this separation was already

present prior to vector delivery and did not reflect a divergent recovery trajectory. The treatment-by-time interaction for behavior was not significant (p=0.5506). At sacrifice, as with fluorodopa PET, striatal TH was remarkable reduced on the lesion side with no differences seen between group. On the lesioned nigra, there was no differences in the number of residual TH-ir cells between the two treatment groups. Together, these data indicate that AAV-mediated PTBP1 knockdown does not convert astrocytes to neurons nor induce nigrostriatal dopaminergic regeneration in a macaque model of Parkinson's disease.

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Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.01/U10

Topic: C.06. Neuromuscular Diseases

Support: FDA Grant UH3FD008137

Title: Patient and Caregiver Perspectives on Communication Impairment and Communication Brain-Computer Interfaces in Amyotrophic Lateral Sclerosis

Authors: J. ASOK KUMAR[1], S. R. MELBY[2,1], L. CLAWSON[3], D. C. TIPPETT[4], C. LIU[5,6,7], *S. KELLIS[1,5,6];
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Abstract: Communication brain-computer interfaces (cBCIs) may restore spoken communication in individuals with amyotrophic lateral sclerosis (ALS) by enabling neural control independent of motor function. However, standardized clinical outcome assessments (COAs) for evaluating cBCI efficacy remain underdeveloped and require input from patients, caregivers, clinicians, researchers, and regulators. Our previous work identified 21 candidate COAs relevant to cBCI evaluation, but no single measure comprehensively captured the multidimensional impact of cBCIs. In the present study, we sought to characterize patient and caregiver perspectives on speech communication impairment, quality of life, and the perceived benefits and risks of cBCIs to inform the development of patient-centered evaluation frameworks. Semi-structured interviews were conducted across three clinical sites (Johns Hopkins University, University of Utah, and Rancho Los Amigos National Rehabilitation Center) with individuals with ALS (n=22), while their caregivers participated in focus groups (n=17). Interviews explored speech changes and functional status, quality of life, and perceived

benefits and risks of cBCIs. Interview transcripts were analyzed using thematic analysis, and structured response analysis was performed to characterize similarity of patient-caregiver perspectives. Thematic analysis identified recurring themes related to progressive speech decline, difficulty being understood, reduced participation in social interactions, communication-related fatigue, caregiver burden, and variable experiences with existing assistive communication technologies. Structured response analysis demonstrated substantial patient-caregiver agreement regarding communication-related challenges, while differences emerged in perceptions of relationship impacts, familiarity with cBCI technologies, and willingness to adopt invasive communication interventions. Participants expressed conditional openness toward cBCIs, particularly as speech impairments worsened, while also highlighting concerns regarding usability, invasiveness, timing of intervention, and expected functional benefit. These findings suggest that communication impairment resulting from speech decline in ALS affects social participation, interpersonal relationships, autonomy, and caregiver burden. Incorporating patient and caregiver perspectives into future evaluation frameworks may support the development of clinically meaningful outcome measures and facilitate future clinical implementation of cBCIs in ALS.

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Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

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Program #/Poster #: PSTR091.02/U11

Topic: C.06. Neuromuscular Diseases

Title: SEALS: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Evaluating Efficacy And Safety Of NX210c In Amyotrophic Lateral Sclerosis (ALS) Patients

Authors: *A. I. JANUS[1], S. MARIE[1], J. LE DOUCE[1], N. REBERGUE[1], P. MESSINA[2], Y. GODFRIN[1];
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Abstract: SEALS: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Evaluating Efficacy And Safety Of NX210c In Amyotrophic Lateral Sclerosis (ALS) Patients**Objectives**NX210c is a chemically synthesized Thrombospondin type 1 repeat (TSR1) analog that demonstrates blood brain barrier (BBB) integrity restorative capacity by increasing the dominant tight junction protein expressed on neurovascular endothelium (claudin-5), exhibits neuroprotective properties and neurotransmission enhancement. Combining these properties, NX210c is a promising drug candidate for several CNS diseases including ALS. **Material and methods**The SEALS Phase 2 clinical trial (NCT 06365216) investigated biomarkers and clinical outcomes in 82 ALS patients randomized and dosed 3-times per week for 4 weeks with intravenous infusion of NX210c at 5, 10 mg/kg or placebo in a 3:3:2 ratio, also stratified by

serum neurofilament light (NfL), a prognostic biomarker of disease activity. A core study followed patients for 3 months thereafter. Primary endpoints included NfL or Qalb (Quotient of albumin conc. in CSF/Blood) changes. Secondary endpoints expanded the analysis of safety, pharmacokinetics and clinical (e.g. Harmonized ALSFRS-R score, Handheld Dynamometry (HHD)) and blood, CSF, urine biomarker indicators. **Results**The safety and tolerability profile of NX210c was good. The half-life of NX210c was 17 min. and no accumulation in the blood as previously observed in healthy volunteers. A dose dependent trend to NfL changes was observed at 4 and 6 weeks and a subgroup of patients decreasing NfL by more than 10% and combined with a Qalb decrease was identified. The slope of ALSFRS-R score calculated from baseline to week 6 was reduced by 0.47 (5mg/kg) and 0.24 points/month (10mg/kg) compared to placebo, mainly due to motor scores. At week 4, at 5mg/kg about 30% of the patients improved or stabilized their HHD in left and right elbow, wrist, knee, and ankle. The up coming 3-month follow up results will be presented during the convention. **Conclusion**According to the preliminary positive signal of effect, NX210c is a drug candidate with combined properties relevant to play a significant role in the treatment of ALS patients. Based on SEALS results, *in silico* modeling will be able to profile the responders and to determine the optimized dose and regimen for next clinical development milestones.

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Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.03/U12

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01 AR077191
ALS Association
UW Stem Cell and Regenerative Medicine Center
UW Foundation

Title: Muscle-targeted Bet1L gene therapy preserves neuromuscular junctions and extends survival in a rat model of familial ALS

Authors: J. GRITZMAN[1], Z. TANG[1], J. KE[1], S. BRADTKE[1], A. LEE[1], W. SHIN[1], ***M. SUZUKI**[1,2];
[1]Comparative Biosci., [2]Stem Cell and Regenerative Med. Ctr., Univ. of Wisconsin Madison, Madison, WI

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive paralysis, muscle atrophy, and ultimately respiratory failure. Although ALS has traditionally been viewed as a motor neuron disease, growing evidence suggests that motor neuron degeneration may occur in a retrograde manner, beginning in the periphery at neuromuscular junctions (NMJs) and skeletal muscle. Our laboratory recently identified the vesicle trafficking protein Bet1L (Bet1 Golgi Vesicular Membrane Trafficking Protein Like) as a novel candidate regulator of NMJ degeneration in ALS (Lynch et al., *Experimental Neurology*, 2022; Eckardt et al., *Frontiers in Neuroscience*, 2025). In the present study, we tested the hypothesis that skeletal muscle overexpression of Bet1L, delivered via adeno-associated virus (AAV), preserves NMJs and motor neurons, thereby improving motor function and survival in a familial ALS rat model (SOD1-G93A transgenic). To achieve specific expression in postmitotic striated muscle cells *in vivo*, we used AAV serotype 9 driven by regulatory elements of the murine muscle creatine kinase gene and the α-myosin heavy chain enhancer. High-titer AAV expressing Bet1L (AAV-Bet1L) was bilaterally injected into the quadriceps, hamstrings, tibialis anterior, and gastrocnemius muscles of presymptomatic ALS rats at 110 days of age. Intramuscular delivery of AAV-Bet1L significantly enhanced motor function in the treated limbs compared with sham-treated controls. This effect was demonstrated by improved scores on the weekly Basso-Beattie-Bresnahan (BBB) locomotor rating scale test and increased grip strength. At the symptomatic stage (152 days of age), histological analyses demonstrated a significant preservation of NMJ integrity in muscles receiving AAV-mediated Bet1L expression. Furthermore, in an independent cohort of ALS rats receiving additional forelimb and epaxial muscle injections, intramuscular AAV-Bet1L treatment significantly prolonged survival. Collectively, these findings identify Bet1L as a critical muscle-specific regulator of NMJ stability and disease progression in ALS, highlighting its potential as a therapeutic target.

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Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.04/U13

Topic: C.06. Neuromuscular Diseases

Support: NIH RF1NS127407
Target ALS Foundation BB-2024-C1-L3
LifeArc LA-MNDDRP-2024-02

Title: Cardiac glycosides mitigate ALS/FTD pathology across in vitro and in vivo disease models

Authors: *H. KORBEY[1], C. MARQUES[1], M. YATES[1], S. CHEN[1], L. SUN[1], P. SENARATNE[1], V. S. VILLARREAL[1], I. FLESSAS[1], R. MEIR[1], H. AHANGER[1], B. SCHLINKMAN[2], C. VIETS[1], N. RAMESH[1], C. BANNERMAN[1], A. H. HELD[1], M. W. ALBERS[1], I. M.-C. CHIU[3], L. PETRUCELLI[4], A. N. COYNE[5], C. LAGIER-TOURENNE[1], B. WAINGER[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by a confluence of cellular dysfunction including perturbation of RNA binding proteins, proteostasis, and axonal processing. Approaches to modeling the disease have generally focused on a single locus of pathology, for example either loss of the RNA-binding protein TDP-43 from the nucleus or the accumulation of insoluble cytoplasmic aggregates of phosphorylated TDP-43. Here, we employed independent phenotypic screens and mouse models to identify mitigators of multiple aspects of ALS pathobiology. We conducted high-content phenotypic screens using two disease-relevant stressors to identify compounds that rescued cell survival and neurite outgrowth in human iPSC-derived neurons. The first screen modeled the toxicity of arginine-containing dipeptide repeat proteins (DPRs) associated with the most common genetic form of ALS, a hexanucleotide repeat expansion of the C9orf72 gene. The second screen used bortezomib (BTZ), an inhibitor of the 26S proteasome, to induce endogenous TDP-43 mislocalization and dysfunction without direct genetic alteration of TDP-43. The cardiac glycosides digoxin and ouabain emerged as lead hits in these two screens, showing neuroprotective effects at sub-micromolar doses in both models of ALS. Focusing on FDA-approved digoxin, we validated its activity across multiple human neuronal lines and defined its mechanism of action through pharmacologic and genetic perturbation of the Na^+/K^+-ATPase. We found that digoxin mitigated ALS pathology in iPSC neurons by enhancing autophagic flux and preventing an apoptotic signaling cascade downstream of proteotoxic stress. To validate the neuroprotective impact of digoxin treatment *in vivo*, we used both an established mouse model of DPR toxicity and a novel proteasome-based mouse model. We found that digoxin treatment alleviated ALS-associated behavioral phenotypes, corrected TDP-43 mislocalization, and mitigated neuromuscular junction degeneration in a proteasome inhibition model of ALS. In this work, we identify Na^+/K^+-ATPase modulation as a shared node of neuronal resilience across ALS-relevant stress paradigms and establish cardiac glycosides as candidate therapeutics for investigation in ALS.

Disclosures: H. Korbey: None. **C. Marques:** None. **M. Yates:** None. **S. Chen:** None. **L. Sun:** None. **P. Senaratne:** None. **V.S. Villarreal:** None. **I. Flessas:** None. **R. Meir:** None. **H. Ahanger:** None. **B. Schlinkman:** None. **C. Viets:** None. **N. Ramesh:** None. **C. Bannerman:** None. **A.H. Held:** None. **M.W. Albers:** None. **I.M. Chiu:** None. **L. Petrucelli:** None. **A.N. Coyne:** None. **C. Lagier-Tourenne:** None. **B. Wainger:** None.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.05/U14

Topic: C.06. Neuromuscular Diseases

Title: A Novel Spinal Motor Neuron-Restricted hTDP-43ΔNLS Mouse Model of ALS

Authors: *D. JIANG[1], H. LIU[2], C. X. WANG[5], X. LU[1], R. LEIB[1], D. LIU[3], Y. HU[4]; [1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Palo Alto, CA, ; [3]Stanford Ophthalmology, [4]Dept. of Ophthalmology, Stanford Univ., Palo Alto, CA; [5]Washington Univ. in St. Louis, St. Louis, MO

Abstract: Aberrant cytoplasmic accumulation of TAR DNA-binding protein 43 (TDP-43) is a pathological hallmark of most amyotrophic lateral sclerosis (ALS) cases. Although overexpressing human TDP-43 with a deleted nuclear localization signal (hTDP-43ΔNLS) in mice recapitulates the cytoplasmic mislocalization observed in ALS, existing models generally rely on broad or non-selective expression in all types of neurons or cells, limiting their ability to appreciate cell-autonomous effects. We developed a method to selectively overexpress spinal motor neuron-specific mislocalization of hTDP-43 into cytoplasm, by intrathecally injecting a Cre-dependent pAAV-PHP.eB-CAG-DIO-hTDP-43ΔNLS virus into 4-week-old B6;129S6-Chattm2(cre)Lowl/J transgenic mice. CHAT-dependent hTDP-43ΔNLS transgenic mice exhibited robust hindlimb clasping as early as 2 weeks post-injection (2wpi), indicating early motor dysfunction. Consistent with this phenotype, the mice showed ALS-like behavioral deficits, including reduced grip strength and impaired performance in rotarod and wire hang tests at 4wpi. Kinematic gait analysis is capable of detecting subtle locomotor abnormalities with high precision but has been rarely used in ALS studies. We optimized this approach for ALS models, enabling detailed characterization of multiple aspects of locomotor dysfunction in our model. Hindlimb kinematic analysis further confirmed locomotor impairment, revealing reduced hindlimb joint heights, shortened stride length, and impaired hindlimb support. These motor deficits were supported by marked peripheral neuromuscular pathology, as shown by sciatic nerves axonal loss and degeneration, muscle atrophy, reduced compound muscle action potential amplitudes (CMAP), and pronounced neuromuscular junction (NMJ) denervation and structural disruption. Collectively, we established a novel spinal motor neuron-restricted hTDP-43ΔNLS mouse model that recapitulates key behavioral and pathological features of ALS. This model provides a valuable platform for investigating cell-autonomous mechanisms and potential therapeutic targets.

Disclosures: D. Jiang: None. **H. Liu:** None. **C.X. Wang:** None. **X. Lu:** None. **R. Leib:** None. **D. Liu:** None. **Y. Hu:** None.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.06/U15

Topic: C.06. Neuromuscular Diseases

Support: National Institute of Health
Department of Defense

Title: Determining the therapeutic window of an AAV gene therapy to mitigate TDP-43 cryptic splicing

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[1]Dept. of Pathology, [2]Pathology, [3]Pathology, Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Loss of TAR DNA-binding protein 43 kDa (TDP-43) nuclear function represents a central pathogenic mechanism in amyotrophic lateral sclerosis (ALS), a progressive and fatal neurodegenerative disease that currently lacks disease modifying therapy. Previously, we showed that intravenous delivery of CTR - a fusion of TDP-43's N-terminal RNA recognition and nuclear localization domains with a RAVER1-derived splicing repressor - by the blood-brain barrier (BBB) permeable AAV.PHP.eB capsid to a mouse model of ALS (ChAT-Cre;Tardbp$^{f/f}$ mice) during early symptomatic stage (one month of age) rescues motor neuron disease. To determine the extent of the therapeutic window, we treated these mice at a later timepoint where the disease has already progressed, reflecting the clinical context of symptomatic treatment. Male and female littermates, including ChAT-Cre;Tardbp$^{f/+}$ (control) and ChAT-Cre;Tardbp$^{f/f}$ (knockout) mice, were randomly divided and administered AAV-PHP.eB-GFP (control) or AAV-PHP.eB-CTR via lateral tail vein injection at 3 months of age, a timepoint of established motor neuron loss in this model. Intravenous administration of AAV.PHP.eB-CTR resulted in a reduction in motor deficits associated with TDP-43 depletion. We show that AAV.PHP.eB-CTR-treated ChAT-Cre;Tardbp$^{f/f}$ mice exhibited significant improvement in grip strength as compared to their AAV.PHP.eB-GFP-treated counterparts. AAV.PHP.eB-CTR also attenuated age-related weight loss and extended the lifespan of ChAT-Cre;Tardbp$^{f/f}$ mice. To date, these initial results suggest a wide window of therapeutic opportunity for this AAV gene therapy designed to restore TDP-43 function for ALS.

Disclosures: O. Sitzman: None. **A. Peethambaran Mallika:** None. **P.C. Wong:** None.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.07/U16

Topic: C.06. Neuromuscular Diseases

Support: R21NS128630 to DRS and MG
R21NS127028 to DRS
R01NS137233 to DRS
R01NS097903 to DRS
R35NS127253 to SMP
R61/R33NS124965 to DRS and SMP
Harrington Discovery Institute Rare Disease Scholarship to DRS

Title: Genetic and antisense-mediated reduction of STAU1 rescues TDP-43 proteinopathy phenotypes

Authors: *D. R. SCOLES, S. PAUL, W. DANSITHONG, K. FIGUEROA, J. LI, M. M. GANDELMAN, S. M. PULST;
Univ. of Utah, Salt Lake City, UT

Abstract: TDP-43 proteinopathies are characterized by impaired RNA metabolism, disrupted proteostasis, and progressive neurodegeneration. The RNA-binding protein STAU1 is abnormally elevated in multiple neurodegenerative disease models and has been linked to defects in autophagy and stress response pathways. Previously, we found that STAU1 is overabundant in amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) patient fibroblasts, as well as in mouse models of these diseases. STAU1 overabundance disrupts autophagic flux through its direct binding to the 5'-UTR of *MTOR*, leading to its increased translation and hyperactivation. Because STAU1 contributes to cellular dysfunction associated with TDP-43 pathology, here we evaluated genetic and antisense-mediated reduction of STAU1 as a therapeutic strategy in TDP-43 mouse models. Screening of antisense oligonucleotides (ASOs) targeting human *STAU1* identified ASO45, which also recognizes mouse *Stau1*. Intracerebroventricular (ICV) administration of ASO45 to Thy1-TDP-43 Tg/+ mice reduced STAU1 levels and normalized markers associated with autophagy and neurodegeneration in spinal cord, including mTOR, p62, NeuN, and ChAT, determined by western blotting. Treatment shortly after birth significantly prolonged survival by >15%. Because TDP-43 regulates RNA metabolism and abnormal splicing is a hallmark of TDP-43 proteinopathy, we next evaluated transcriptomic alterations associated with cytoplasmic TDP-43 accumulation. In Prp-TDP-43(Q331K) Tg/+ mice, ICV delivery of ASO45 significantly improved aberrant splicing of *Sort1*, *Kcnip2*, and *Ahi1* TDP-dependent transcripts. To further examine the contribution of STAU1 to disease phenotypes, Prp-TDP-43(Q331K) mice were crossed with *Stau1* haploinsufficient mice (*Stau1*+/−). Genetic reduction of STAU1 significantly improved motor performance, including rotarod behavior at 8, 12, 16, and 20 weeks of age, as well as grip strength at 14 and 20 weeks. These findings demonstrate that reducing STAU1 ameliorates molecular and motor abnormalities associated with TDP-43 proteinopathy. Improvements in autophagy-related pathways and restoration of TDP-43-dependent RNA processing support a functional role for STAU1 in disease

pathogenesis. Collectively, these data identify STAU1 as a promising therapeutic target for ALS and related TDP-43 proteinopathies.

Disclosures: D.R. Scoles: None. **S. Paul:** None. **W. Dansithong:** None. **K. Figueroa:** None. **J. Li:** None. **M.M. Gandelman:** None. **S.M. Pulst:** None.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.08/U17

Topic: C.06. Neuromuscular Diseases

Support: I-DEMO REGION 2301721701

Title: NX210c, an innovative peptide with neurovascular and peripheral effect in ALS

Authors: A. JANUS, S. MARIE, J. LE DOUCE, N. REBERGUE, ***Y. GODFRIN**;
Axoltis Pharma, Lyon, France

Abstract: Background NX210c is a 12 amino acid peptide designed from subcommissural organ spondin, a glycoprotein essential for nervous system development. β1-integrin has been identified as its most important receptor. Increasing evidence suggests that disruption of blood-brain and blood-spinal cord barrier integrity may contribute to ALS pathophysiology, alongside other pathogenic mechanisms, leading to neuroaxonal loss. In this context, NX210c links activity across the neurovascular unit, extracellular matrix-cell interactions, and neural cells, thereby providing a unified basis for barrier stabilization and synaptic modulation.
Method The SEALS Phase 2 clinical trial (NCT 06365216) investigated biomarkers and clinical outcomes in 82 ALS patients randomized to doses of 5 mg/kg, 10 mg/kg or placebo in a 3:3:2 ratio, stratified by neurofilament light (NfL, in serum), a prognostic biomarker of disease activity. The co-primary endpoints were change in NfL or Q albumin ratio 2 weeks following a 3-times per week for 4 weeks treatment with intravenous infusion of NX210c (or placebo). Secondary endpoints included fluid biomarkers, clinical and functional outcomes, including bilateral strength using handheld dynamometry (HHD) in the upper and lower limbs (elbow flexion, wrist extension, knee extension, ankle dorsiflexion)
Results At week-6, a decrease of more than 10 NfL from baseline was observed in a subgroup of patients and was associated with Qalb decrease in 43% and 87.5% of patients at 5 mg/kg and 10 mg/kg, respectively. At the end of treatment, about 30% of the patients treated at 5mg/kg have a HHD improvement (left and right) in the 4 muscle categories.
Conclusion Extending the β1 integrin based framework across the blood-neural barrier axis, early changes in HHD observed at end of treatment (4 weeks) in a subset of NX210c-treated ALS patients could be consistent with peripheral repair biology and support a potential effect at residual motor units. These findings localize early clinical effects of NX210c as a novel therapeutic to the peripheral motor unit—where reinnervation remains actionable—with possible

adjunctive contributions through neurovascular stabilization and reduced excitotoxic stress over time.

Disclosures: A. Janus: 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.; Axoltis Pharma. **S. Marie:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **J. Le Douce:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **N. Rebergue:** A. Employment/Salary (full or part-time):; Axoltis Pharma. **Y. Godfrin:** A. Employment/Salary (full or part-time):; Axoltis Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axoltis Pharma.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.09/U18

Topic: C.06. Neuromuscular Diseases

Title: Mitochondrial Complex I Modulator C273 Improves Redox Balance and Mitochondrial Resilience in ALS Patient-Derived LCLs

Authors: *S. GRIJALVA[1], S. TRUSHIN[2], M. OSTROOT[2], T. NGUYEN[1], E. TRUSHINA[3]; [2]Neurol., [3]Dept. of Neurol., [1]Mayo Clin., Rochester, MN

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by the progressive degeneration of upper and lower motor neurons. Mitochondrial dysfunction, impaired redox homeostasis, and oxidative DNA damage contribute to ALS. Lymphoblastoid cell lines (LCLs) from ALS patients provide a model to assess disease-related mitochondrial and stress-adaptation defects. C273 is a brain-penetrant small molecule mitochondrial complex I (mtCI) modulator that is optimized for clinical application and has shown mitochondrial restoration in different models of neurodegeneration. Treatment with C273 activates neuroprotective mechanisms that enhance antioxidant defenses, suppresses inflammatory signaling, induces autophagy, and increases mitochondrial biogenesis and turnover. Here, we tested whether C273 improves resilience to oxidative stress in ALS LCLs. We first assessed whether C273 treatment induces toxicity in ALS LCLs. LCLs from sporadic ALS patients were treated with different concentrations of C273 for 24 hrs. We found that treatment was nontoxic up to 100 μM. We next determined whether pretreatment with C273 reduces cell death in response to acute H_2O_2-induced oxidative stress. Oxidative injury was assessed using viability assays, Comet assay, and γH2AX phosphorylation. Mechanism of action was evaluated assessing AMPK-dependent signaling and antioxidant responses by Western blotting for pAMPK, pACC, NRF2, catalase, thioredoxin, and DNA damage/apoptosis markers. To address the effect of C273 in mitochondrial bioenergetics, a Seahorse mitochondrial stress test was used to assess basal, ATP-linked, maximal, and spare respiration. Biogenesis and OXPHOS remodeling were

evaluated by Western blot analysis of PGC-1α, SIRT3 and respiratory chain proteins. C273 pretreatment improved resistance to acute H_2O_2-induced oxidative injury in ALS LCLs, with variable responses among patient lines. Preliminary Western blot analyses suggest that by modulating mtCI and activating AMPK-linked antioxidant defenses, C273 may increase cellular resilience to oxidative stress, improve mitochondrial adaptive capacity, and enhance antioxidant defense. C273 reduced oxidative DNA damage and attenuated γH2AX phosphorylation in responsive LCLs, suggesting suppression of genotoxic stress. Our findings support a model in which C273 induces rapid redox preconditioning in ALS patient-derived LCLs. These studies support further evaluation of weak mtCI modulation as a therapeutic strategy for ALS.

Disclosures: S. Grijalva: None. **S. Trushin:** 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. **M. Ostroot:** 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. **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. **E. Trushina:** 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..

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.10/U19

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01EY030072,
NIH Grant R01EY036519
Foundation Flighting Blindness TA-NMT-0423-0851-MITOCHEM-TRAP

Title: Restoration of FUS subcellular Localization and reduction of ALS/FTD Mutation-Induced toxicity by the Oxindole MC16

Authors: *S. GAUR[1], W. MYERS[2], P. THWIN[3], H. ZHU[4], B. ROHRER[5];
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Abstract: Fused in sarcoma (FUS) is an RNA-binding protein that is primarily located to the nucleus and plays essential roles in RNA processing. Mutations in FUS are a well-established cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), with most disease-associated variants occurring within the C-terminal nuclear localization sequence. These mutations disrupt nuclear import, leading to abnormal accumulation of FUS in the cytoplasm and the formation of pathogenic inclusions. Importantly, the degree of cytoplasmic FUS mislocalization has been linked to disease progression in patients carrying FUS mutations, highlighting the importance of restoring proper subcellular distribution. We earlier identified the oxindole compound MC16 as a neuroprotective molecule. Here, we examined its molecular target and mechanism of action. Using click chemistry-based target identification and proteomic analysis, we identified FUS as the main cellular target of MC16. Direct binding of MC16 to the RNA recognition motif of FUS was further validated through biophysical studies, which also established the binding affinity of the interaction. Treatment with MC16 significantly increased nuclear localization of multiple ALS/FTD-associated FUS mutants, including R495X, R518K, and R521C/G, in cell models. Similar effects were observed in Drosophila expressing mutant FUS. In these in vivo models, MC16 improved ommatidial organization and restored eye pigmentation, indicating protection against mutant FUS-induced neurodegenerative phenotypes. Mechanistically, restoration of nuclear FUS by MC16 was not blocked by the proteasome inhibitor MG132, suggesting that mutant FUS is redirected to the nucleus rather than eliminated through degradation. Furthermore, MC16 improved interactions between wild-type and mutant FUS proteins, supporting an associated transport mechanism in which mutant FUS is co-imported into the nucleus through association with wild-type FUS. Collectively, these findings identify MC16 as a promising modulator of FUS trafficking and support its therapeutic potential for FUS-associated ALS and FTD.

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Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.11/U20

Topic: C.06. Neuromuscular Diseases

Title: Neuroprotective Effects of SIR2501, an Allosteric SARM1 Inhibitor, in Preclinical Studies of ALS, Glaucoma, and Ischemic Stroke

Authors: *W. FAN[1], Q. WANG[1], L. YU[1], L. LIU[1], N. CHEN[1], Y. XU[2], S. AGARWAL[3]; [1]Sironax, Beijing, China; [2]Sironax, Noblesville, MA; [3]Sironax, Sharon, MA

Abstract: SARM1 is a key executioner of pathological axonal degeneration and a therapeutic target for various neurodegenerative disorders. We evaluated whether SIR2501, a small-molecule SARM1 inhibitor, provides neuroprotection across preclinical models of amyotrophic

lateral sclerosis (ALS), glaucoma, and ischemic stroke. In the TDP43^{Q331K} ALS mouse model, effect of SIR2501-treatment was compared with that of vehicle-treatment and wild-type controls. At 12-13 weeks of age, plasma neurofilament light chain (NfL) was approximately 10-fold higher in TDP43^{Q331K} mice than that in wild-type controls. After 21 days of SIR2501 treatment, we observed plasma NfL reduction by 30-50%, preserved neuromuscular junction (NMJ) integrity, increased fully innervated NMJs from 19.4% to 49.8%, and reduced denervated NMJs from 28.3% to 11.5%. SIR2501 also attenuated functional impairment in gait measures, including stride length and print position. These pharmacological findings were supported by a longitudinal genetic study in TDP43^{Q331K} /*Sarm1*$^{-/-}$ mice, in which *Sarm1* deletion reduced plasma NfL by approximately 50% in both sexes and significantly reduced NMJ denervation. In an optic nerve crush model of glaucoma, SIR2501 produced dose-dependent axonal protection of optic nerve. In a target-engagement study, nerve protection of 23%, 49%, and 74% was associated with cADPR inhibition of 13%, 30%, and 56%, respectively, supporting a quantitative relationship between SARM1 pathway inhibition and axonal protection. In a non-human primate permanent middle cerebral artery occlusion model of ischemic stroke, plasma NfL followed a trajectory consistent with that reported in patients with stroke and was reduced by SIR2501 treatment. Reduced plasma NfL was associated with smaller lesion size and improved behavioral recovery. Together, these data show that SIR2501 reduces neuronal injury biomarkers, preserves neuronal and axonal integrity, and attenuates functional deficits across models of chronic neurodegeneration, optic nerve injury, and acute ischemic brain injury.

Disclosures: W. Fan: A. Employment/Salary (full or part-time):; SIRONAX. **Q. Wang:** A. Employment/Salary (full or part-time):; SIRONAX. **L. Yu:** A. Employment/Salary (full or part-time):; SIRONAX. **L. Liu:** A. Employment/Salary (full or part-time):; SIRONAX. **N. Chen:** A. Employment/Salary (full or part-time):; SIRONAX. **Y. Xu:** A. Employment/Salary (full or part-time):; SIRONAX. **S. Agarwal:** A. Employment/Salary (full or part-time):; SIRONAX.

Poster

PSTR091: ALS and Motor Neuron Diseases: Therapeutics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR091.12/U21

Topic: C.06. Neuromuscular Diseases

Title: SIR2501, a Novel SARM1 Inhibitor, Demonstrates Favorable Safety and Early Evidence of Biological Activity in Patients With Amyotrophic Lateral Sclerosis

Authors: S. AGARWAL[1], L. SONG[2], B. WANG[2], S. WU[2], D. GRACHEV[1], D. FAN[4], J. QIU[2], V. LATIFI[3], ***A. RAJARETHINAM**[1], W. FAN[2];
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Abstract: Axonal degeneration is a central driver of functional decline in amyotrophic lateral sclerosis (ALS). Activation of the neuronal NAD^+ hydrolase SARM1 triggers rapid NAD^+

depletion and ATP loss, initiating irreversible axonal breakdown. Genetic and pharmacologic inhibition of SARM1 prevents axonal injury in multiple ALS-relevant models. SIR2501 is a novel, brain-penetrant SARM1 inhibitor in clinical development for ALS. We assessed its safety, pharmacokinetics (PK), and early pharmacodynamic activity in healthy adults. We are currently evaluating safety and preliminary clinical activity in ALS patients. In a randomized, double-blind, placebo-controlled first-in-human study in healthy participants (n=88), multiple doses were tested. In this study SIR2501 was well tolerated, with no serious adverse events, no Grade ≥3 treatment-emergent events, and only mild to moderate asymptomatic laboratory abnormalities that resolved without intervention and were adjudicated as unrelated to study drug by blinded investigators. SIR2501 demonstrated rapid absorption, prolonged elimination half-life, moderate accumulation, and linear, time-independent PK supporting once-daily dosing and enabling PK extrapolation across global populations. In an ongoing global Phase 1b/ 2 open-label ALS study, twelve patients have been treated at multiple dose levels. Safety is prospectively reviewed by an independent Safety Review Committee at defined timepoints. Early activity assessments include blood neurofilament light chain (NfL), a biomarker of axonal injury, and ALS Functional Rating Scale-Revised (ALSFRS-R) scores, to evaluate potential effects on neurodegeneration and functional decline. Across completed ALS cohorts, SIR2501 has shown an acceptable safety profile with no dose-limiting toxicities, so far, no serious adverse events, and no clinically meaningful ECG, vital-sign, or hematologic abnormalities; all adverse events have been observed as unrelated to study drug. The preliminary results demonstrate that SIR2501 is well tolerated in ALS patients, achieves predictable PK which is consistent with target engagement and suggest early evidence of biological and clinical activity. Together, the results support continued development of SIR2501 as a first-in-class therapeutic candidate aimed at interrupting SARM1-mediated axonal degeneration, a key pathogenic mechanism in ALS.

Disclosures: S. Agarwal: A. Employment/Salary (full or part-time):; SIRONAX. **L. Song:** A. Employment/Salary (full or part-time):; SIRONAX. **B. Wang:** A. Employment/Salary (full or part-time):; SIRONAX. **S. Wu:** A. Employment/Salary (full or part-time):; SIRONAX. **D. Grachev:** 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.; SIRONAX. **D. Fan:** A. Employment/Salary (full or part-time):; Peking University Third Hospital. **J. Qiu:** A. Employment/Salary (full or part-time):; SIRONAX. **V. Latifi:** A. Employment/Salary (full or part-time):; SIRONAX. **A. Rajarethinam:** A. Employment/Salary (full or part-time):; SIRONAX. **W. Fan:** A. Employment/Salary (full or part-time):; SIRONAX.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.01/Web Only

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

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The Snyder Private Foundation
The Wilstein Private Foundation
The Gordon Private Foundation
The Jona Goldrich Center Alzheimer's Disease

Title: Epigenetic repression by histone H3 lysine 9 trimethylation drives synaptic dysfunction across the brain-retina axis in Alzheimer's disease

Authors: *D.-T. FUCHS[1], J.-P. S. VIT[1], A. RENTSENDORJ[1], Y. KORONYO[1], B. GAIRE[1], S. SHAHIN[1], O. CHEPURNA[1], L. SCHNEIDER[2], M. KLEINMAN[3], M. FAHNESTOCK[4], M. MIRZAEI[5], K. BLACK[1], M. KORONYO-HAMAOUI[1];
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Abstract: Epigenetic dysregulation is emerging as mechanistic driver of neurodegenerative disorders, including Alzheimer's disease (AD). Among histone modifications, tri-methylation of histone H3 lysine 9 (H3K9me3), a constitutive heterochromatin mark, represses activity-dependent synaptic genes and constrains neuronal plasticity. Indeed, H3K9me3, catalyzed by methyltransferase SUV39H1, is elevated in both aged and AD brains. Despite the reversible nature of epigenetic modifications, it remains unclear whether reducing H3K9me3 can ameliorate AD-associated pathology and functional deficits. Notably, AD pathology extends to the neurosensory retina, where amyloid-β (Aβ) and hyperphosphorylated tau accumulation, neuroinflammation, vascular injury, and synaptic degeneration parallel cerebral changes. Because the retina is an accessible CNS extension, conserved epigenetic programs across the brain-retina axis may provide mechanistic insight and enable noninvasive biomarker development. Here, we quantified H3K9me3 and mapped associated proteomic networks in postmortem brains and matched retinas from cognitively normal (CN) individuals and patients with mild cognitive impairment (MCI due to AD) and AD dementia. To test functional relevance, we pharmacologically inhibited SUV39H1 in two transgenic mouse models of AD (APPswe/PS1dE9 and APPswe/tauP301L/PS1^{tm1Mpm}) and performed behavioral, biochemical, proteomic, histological, and blood-based immunophenotyping analyses. We found that brain and retinal H3K9me3 was elevated in MCI and further increased in AD dementia, scaling with cognitive decline, and Aβ/tau pathology. Proteomic signatures in AD cortex and retina revealed enrichment of heterochromatin-forming and histone modifying pathways, and predicted SUV39H1 hyperactivity and H3K9 trimethylation. In AD mouse models, SUV39H1 inhibition lowered cerebral H3K9me3, re-established brain and retina neuroimmune and synaptic proteostasis. This epigenomic shift attenuated gliosis, amyloid/tau burden, dendritic spine loss, and improved visuo-cognitive functions. Mechanistically, these effects converged on reactivation of a trophic-immune signaling axis centered on neurosecretory VGF and the extended granin family, which coordinates synaptic function and microglial phenotype. Together, these findings position H3K9me3 as a shared epigenetic driver of AD-related dysfunction across the brain-

retina axis and support its targeting as a therapeutic strategy while highlighting retinal epigenomic profiling as a noninvasive window into AD-associated chromatin changes.

Disclosures: D. Fuchs: None. **J.S. Vit:** None. **A. Rentsendorj:** None. **Y. Koronyo:** None. **B. Gaire:** None. **S. Shahin:** None. **O. Chepurna:** None. **L. Schneider:** None. **M. Kleinman:** None. **M. Fahnestock:** None. **M. Mirzaei:** None. **K. Black:** Other; Co-Chairman and shareholder, Fortem. **M. Koronyo-Hamaoui:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.02/U23

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

Support: NIH Grant R01AG056478
NIH Grant R01AG055865
NIA Grant AG056478-04S1
Goldrich and Snyder Foundations
Ray Charles Foundation

Title: Astrocytic ERα/ERβ imbalance in the retina and brain drives female biased gliosis and neurodegeneration in Alzheimer's disease

Authors: *S. SHAHIN[1], J.-P. VIT[1], A. RENTSENDORJ[1], D.-T. FUCHS[1], N. SWERDLOW[1], B. GAIRE[1], E. ROBINSON[1], L. HAGERMAN[1], A. WILLIAMS[1], L. SCHNEIDER[2], M. MIRZAEI[3], K. BLACK[1], Y. KORONYO[1], M. KORONYO-HAMAOUI[1];
[1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]USC, Los Angeles, CA; [3]Macquarie Univ., Sydney, Australia

Abstract: Women have about twice lifetime risk for Alzheimer's disease (AD) compared with men, yet the biological mechanisms underlying female vulnerability remain poorly understood. To identify sex-specific pathological pathways across the retina-brain axis, we integrated clinicopathological, histopathological, and proteomic datasets from paired retina and brain tissues of 182 donors with normal cognition (NC; n=30), mild cognitive impairment (MCI; n=18), and AD dementia (n=86). Statistical analyses included two-way ANOVA with Bonferroni correction, Student's *t*-tests, and Pearson or Spearman correlation analyses. Female AD retinas exhibited greater tau pathology, including increased p-tau and NFTs (MC1, ~1.4-fold), paralleling sex differences in cerebral NFT burden, despite comparable Aβ pathology between sexes. Retinal $A\beta_{42}$ strongly correlated with cerebral Aβ plaque burden, Braak stage, and ABC score (r=0.4-0.6), and more strongly associated with cognitive decline in females (r=0.6). Retinal oligomeric tau showed robust relationship with cognitive impairment in females (r=0.7). Strikingly, AD females displayed significantly greater retinal microgliosis and astrogliosis (IBA1, ~1.4-fold; GFAP, ~1.2-fold), which closely associated with retinal $A\beta_{42}$ and oligomeric

tau burden (r=0.83-0.90) and cognitive decline (r=0.47 to -0.70). In contrast, retinal vascular $A\beta_{40}$ was elevated (~1.7-fold) and more strongly linked to cognitive deficit in AD males, whereas in females it was strongly associated with retinal microgliosis (r=0.8). Retinal endothelial tight-junction loss correlated with cerebral amyloid angiopathy (CAA) severity (r=0.8), particularly in males. Proteomic analyses identified estrogen signaling as one of the most significantly dysregulated pathways in both retina and brain, with estrogen receptor alpha (ERα) and beta (ERβ) emerging as top predicted upstream regulators. Immunofluorescence and immunoblot analyses revealed relative preservation and astrocytic enrichment of ERα, particularly in females, alongside progressive ERβ depletion across both tissues. ERβ levels declined by 20-24% in MCI and 36-53% in AD relative to controls, with AD females exhibiting 24-27% lower retinal and cortical ERβ expression than AD males. Importantly, ERβ loss and an increased astrocytic ERα/ERβ ratio were strongly associated with heightened gliosis, tau pathology, and neurodegeneration, particularly in females. These findings identify estrogen receptor dysregulation as a shared retina-brain mechanism of AD and suggest that astrocytic ERα/ERβ imbalance contributes to female-biased neuroinflammation and neurodegeneration.

Disclosures: S. Shahin: None. **J. Vit:** None. **A. Rentsendorj:** None. **D. Fuchs:** None. **N. Swerdlow:** None. **B. Gaire:** None. **E. Robinson:** None. **L. Hagerman:** None. **A. Williams:** None. **L. Schneider:** None. **M. Mirzaei:** None. **K. Black:** None. **Y. Koronyo:** None. **M. Koronyo-Hamaoui:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.03/Web Only

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

Support: NIH Grant: R01 AG075998
Alzheimer's association grant AARG-NTF-21-84658
R01AG075998-05S1

Title: Chlamydia pneumoniae Infection Promotes Neuroinflammation and Cognitive Dysfunction via NLRP3 inflammasome

Authors: *L. SUBEDI[1], J.-P. S. VIT[2], D.-T. FUCHS[3], D. MARTINON[7], M. V. LANE[8], B. GAIRE[4], S. SHAHIN[4], M. MIRZAEI[9], Y. KORONYO[3], M. ARDITI[5], M. KORONYO-HAMAOUI[3], T. CROTHER[6];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that lacks effective disease-modifying therapies, highlighting the need for new mechanistic insights and therapeutic strategies. Increasing evidence suggests that chronic infection may contribute to AD pathogenesis, although causal relationships remain incompletely defined. Here, we demonstrate that intranasal infection with *Chlamydia pneumoniae* (Cpn) induces sustained neuroinflammation and progressive cognitive decline in wild-type mice. Cpn gains access to the brain via the olfactory pathway, leading to pronounced microgliosis and astrogliosis in the cortex and hippocampus, accompanied by elevated pro-inflammatory cytokines and activation of the NLRP3 inflammasome. Long-term infection results in persistent impairments in spatial and working memory, along with reduced levels of neurotrophic and synaptogenic factors, and a loss of excitatory synapses, thereby recapitulating key features of AD-like cognitive dysfunction. These findings are further supported by proteomic and single-nuclear RNA sequencing analyses of the brain cortex. Furthermore, microglia-specific deletion of NLRP3 abolishes neuroinflammation and rescues memory impairments, identifying microglial inflammasome activation as a central mechanistic driver. Importantly, early antibiotic intervention targeting Cpn reverses long-term cognitive deficits, establishing a direct and reversible causal role for infection. Collectively, these findings define a tractable, infection-driven pathway linking peripheral infection to AD-like neurodegeneration and highlight both Cpn and NLRP3 as promising therapeutic targets.

Disclosures: L. Subedi: None. **J.S. Vit:** None. **D. Fuchs:** None. **D. Martinon:** None. **M.V. Lane:** None. **B. Gaire:** None. **S. Shahin:** None. **M. Mirzaei:** None. **Y. Koronyo:** None. **M. Arditi:** None. **M. Koronyo-Hamaoui:** None. **T. Crother:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.04/U24

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

Support: American Parkinson's Disease Association
NC State University Start Up

Title: Neuroinflammation following SARS-CoV-2 Infection

Authors: *H. CROY, J. EELLS;
Mol. Biomed. Sci., North Carolina State Univ., Raleigh, NC

Abstract: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, which causes COVID-19, has infected over 700 million people worldwide resulting in 7 million deaths. Following recovery from SARS-CoV-2 infection, some individuals persistent symptoms, that can range from respiratory to neurological symptoms, has been described as long-COVID or PASC (post-acute sequelae of COVID19). Currently, how SARS-Cov-2 infection affects the

brain has not been fully elucidated. Our previous data demonstrated, using K18 human angiotensin converting enzyme 2 (K18-hACE2) transgenic mice, that ten days post infection of SARS-CoV-2 after recovery from a mild-infection, produced inflammatory changes including increased expression of kinin B1 receptor (B1R), IL-6, and TNFa expression within the amygdala, hippocampus, and prefrontal cortex. We also found, in this model, that SARS-CoV-2 could infect the brain. To determine the contribution of neuronal infiltration of SARS-CoV-2 on these inflammatory pathways, we compared K18-hACE2 mice with mice with adeno associated viruses expressing hACE2 to produce a respiratory-confined SARS-CoV-2 infection. Additionally, we will compare neuroinflammation between the USA-1 variant and the omicron BA.5 variant. Peripherally confined SARS-CoV-2 infection can change the virus's neurological qualities such as the neuroinflammation, microglia activation, and cytokines and chemokines produced. Using these models comparative analyses will be conducted to investigate microglial and astrocyte activation, B1R, TNFa, and Il-6 expression within the lung and brain.

Disclosures: H. Croy: None. **J. Eells:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.05/U25

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

Support: NIAID Grant 1 R15 AI156879
(NIGMS) (5P20GM103427)
(RRID: SCR_023539)
INBRE - P20GM103427

Title: Identification of Novel Neuronal Long Non-Coding RNAs in a TMEV-Induced Model of Neurodegeneration via a Multimodal Bioinformatics and Experimental Pipeline

Authors: *A. MARTA[1,2], A. SHIBATA[3];
[2]Med. Microbiology and Immunol., [3]Biol. Dept., [1]Creighton Univ., Omaha, NE

Abstract: Neurotropic viral infections are a significant risk factor for the development of neurodegenerative diseases. Variations in host cell antiviral responses may determine disease susceptibility. Long noncoding RNAs (lncRNAs) have emerged as essential, cell-specific regulators of antiviral pathways that serve diverse regulatory roles by acting as signals, decoys, guides, or scaffolds that interact with DNA, RNA, and proteins to modulate gene expression and chromatin architecture. The objective of this work is to identify novel lncRNAs that contribute to neurodegenerative disease states following viral infection. As proof-of-concept, Theiler's Murine Encephalomyelitis Virus (TMEV), well known for inducing demyelinating disease (IDD) in mice that mimics the pathogenesis of progressive multiple sclerosis in humans was used to develop a multimodal bioinformatics and experimental pipeline for novel lncRNA identification.

The pipeline was initiated by bulk-RNA sequencing of TMEV-infected and uninfected Neuro2A cortical neurons. A total of 6,593 significantly differentially expressed lncRNAs were identified. The pool included 3,549 upregulated and 3,044 downregulated novel lncRNAs. The lncRTPred Python tool was used to predict interactions between the five most significant novel lncRNAs and their genome-wide vM36 transcript sequences, yielding the top 100 predicted mRNA target sequences for each. The RNA Hybrid v 2.1.2 package was used to determine the minimum free energy hybridization between each novel lncRNA and predicted targets. From these findings, six intergenic lncRNAs (lincRNAs) were selected for further study. Intergenic lncRNAs are notable because they can act in trans, modulating large-scale gene expression at distant promoter sites across multiple chromosomes. RT-qPCR confirmed five novel lincRNAs were differentially expressed in TMEV-infected Neuro2a model ($p<0.05$, N=4). To identify the most viable targets for functional analysis, we validated lincRNA expression in vivo using RT-qPCR on TMEV-IDD mouse hippocampal tissue collected during acute neuronal infection (3 days post-infection). This analysis revealed two novel lincRNAs that were significantly upregulated in vivo compared to controls ($p<0.006$, N=5). Using our integrated pipeline, we have identified two novel lincRNAs upregulated during neurotrophic infection. Ongoing work is evaluating the putative mRNA targets and functional relevance of these novel lincRNAs. These studies will deepen our understanding of lncRNA-mediated antiviral neuroimmune responses and seeks to identify novel therapeutic targets for viral-associated neurodegenerative diseases.

Disclosures: A. Marta: None. **A. Shibata:** A. Employment/Salary (full or part-time):; Creighton University.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.06/U26

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

Title: Exercise, Cognitive Training, and Lifestyle Interventions for HIV-Associated Neurocognitive Disorders: A Narrative Review

Authors: *L. E. AZUARA-ALVAREZ[1], S. SAGRERO[2], G. PALOMINO VIZCAINO[3], A. GARCIA-ANACLETO[4];
[1]Univ. Autonoma de Baja California, TIJUANA, Mexico; [2]Univ. Autonoma de Baja California, Tijuana, Mexico; [3]Univ. Autónoma de Baja California, Tijuana, ; [4]UABC, Tijuana.

Abstract: HIV-associatedneurocognitivedisorders (HAND)remainprevalent despitewidespreaduseof combinationantiretroviral therapy. Persistent neuroinflammation, viral reservoirs withinthecentral nervous system, andtreatment-relatedfactors continuetocontributetocognitivedysfunctionaffecting memory, attention, executivefunction, andprocessing speed. Thepresent narrativereview aimedtoidentify recent evidencesupporting non-pharmacologicalinterventions for themanagement of HAND.A literaturesearch was

conductedinPubMedusing combinations of terms relatedtoHIV,neurocognitiveimpairment, HAND, cognitiverehabilitation, exercise, behavioralinterventions, andnon-pharmacological treatments. Articles publishedwithinthelast fiveyears andfocusedoncognitiveoutcomes inpeopleliving with HIV werereviewed.Current evidencehighlights threemajor interventiondomains. First, lifestyle-relatedfactors,including healthy nutrition, adequatesleep, stress management, andengagement incognitively stimulating activities, appear tosupport cognitivereserveandmay reducetheprogressionof neurocognitivedecline. Second, physical activity consistently demonstratespositiveeffects onattention, executivefunction, processing speed, memory, andoverallcognitiveperformanceacross multiplecohorts andinterventionstudies. Third, computerizedcognitivetraining has shownimprovements inworking memory, processing speed, attention,daily functioning, andquality-of-lifemeasures, with individualizedtraining approachesproducing particularly promising outcomes.Although heterogeneity among studies limits thedevelopment of standardizedprotocols,availableevidencesuggests that non-pharmacological interventions represent safeandpotentially effectivecomplementary approaches for individuals living with HAND. Futurecontrolledstudies areneededtoestablish optimal interventionparameters anddeterminelong-term cognitivebenefits.

Disclosures: L.E. Azuara-Alvarez: None. **S. Sagrero:** None. **G. Palomino Vizcaino:** None. **A. Garcia-Anacleto:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.07/U27

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

Title: Age-linked variation in time to onset and humoral readouts in experimental primary amoebic meningoencephalitis

Authors: *M. CHO[1,2,3], M. UMAM[2,3];
[1]Dept. of Parasitology and Tropical Med., Gyeongsang Natl. Univ. Col. of Med., Jinju-si, Korea, Republic of; [2]Dept. of Convergence Med. Sci., Gyeongsang Natl. Univ., Jinju, Korea, Republic of; [3]Dept. of Parasitology and Tropical Med., Inst. of Med. Science, Gyeongsang Natl. Univ. Col. of Med., Jinju, Korea, Republic of

Abstract: *Naegleria fowleri*, a free-living amoeba, causes primary amoebic meningoencephalitis (PAM), arapidly fatal central nervous system infection with a mortality rate exceeding 95%. Despite itsdevastating outcome, the mechanisms underlying age-dependent susceptibility and immuneresponses during PAM remain poorly understood. To investigate the impact of host age on diseaseprogression, an intranasal infection model was established in C57BL/6 mice using virulent *N.fowleri* trophozoites. Young (5-week-old) and mature (9-week-old) mice were monitored forweight loss, neurological signs, and disease progression, which were integrated into a diseaseactivity index (DAI), and survival was evaluated using Kaplan–Meier analysis.

Serum antibodyresponses were assessed by ELISA and western blotting, while immune cell populations in brain-infiltrating leukocytes were characterized by flow cytometry. Histopathological analyses wereperformed on terminal-stage brain tissues. All infected mice ultimately succumbed to PAM;however, marked age-dependent differences in disease kinetics were observed. Young micedeveloped clinical signs earlier (7 dpi) and reached complete mortality by 13 dpi, whereas maturemice showed delayed disease onset (9 dpi) and survived up to 19 dpi. Mature mice also mountedstronger *N. fowleri*-specific IgG and IgA responses than young mice at the sampled time points.Flow cytometric analysis of terminal-stage brains revealed distinct leukocyte infiltration patternsbetween age groups, although these findings likely reflect end-stage disease rather than earlyimmune events. Preliminary histopathological examination demonstrated broadly comparableinflammatory features in terminal-stage brain tissues regardless of age. Collectively, thesefindings indicate that host age significantly influences the kinetics of PAM progression, withyounger mice exhibiting accelerated disease and mature mice showing delayed onsetaccompanied by enhanced humoral responses. Ongoing studies are investigating whether theseimmune differences contribute directly to disease progression or arise as secondary consequencesof age-dependent disease kinetics.

Disclosures: M. Cho: None. **M. Umam:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.08/U28

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

Support: NINDS R01NS122571
UTMB (CIRWH&SCOA) P30 AG024832
UTMB IHII short-term DPRIT program award

Title: Neurotoxicity of Biktarvy: Sensory Neuropathy and Chronic Pain as Underrecognized ART Adverse Effects

Authors: *A. PAL[1], Y. ZHOU[1], H. LI[1], D. AJASIN[2], B. GONG[1], S. VALDEBENITO-SILVA[3], E. EUGENIN[4], S. YUAN[3];
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Abstract: Lifelong use of antiretroviral therapy (ART) helps HIV patients achieve normal lifespan. However. ART is known causally related to the development of neurological comorbidities such as chronic pain (HIV-PAIN) and sensory neuropathy (HIV-SN), the pathogenesis of pain. The representative first line ART regimen, Biktarvy (Bik) is proved to achieve rapid viral suppression and barrier to resistance, containing two nucleoside reverse transcriptase inhibitors (NRTIs), emtricitabine and tenofovir alafenamide and one integrase

strand transfer inhibitor (INSTI), bictegravir. Bik become a cornerstone therapy in US, Europe. We know that the prevalence of HIV-PAIN is 30-62% of 39 million HIV patients, the high prevalence contradicts with the known lower side effects of highly potent single-tablet regimen, such as Bik. To determine whether Bik is algogenic and contributes to HIV-PAIN. In this study, we evaluated algogenic effects of Bik in both sex of mice, including sex difference is consideration that 51% of HIV patients are female who are known to report more pain locations, higher pain rate and less response to analgesics with poorly reasoning mechanisms. We chose oral gavage Bik to mice for 21 days to mimic the long-term Bik clinical use. We use human equivalent dose (1x) to mimic Bik patient daily use and 3x to fully excavate Bik neurotoxicity and to compensate the limited Bik administration time (up to 21 day) in this experiment. We found both 1x and 3x dose of Bik induced mechanical allodynia started at 11-day post Bik gavage and lasted till the end of experiment (21day). With female mice allodynia started earlier and 50% hindpaw withdraw threshold was lower than male mice. Bik-treated mice also developed heat and cold hyperalgesia. However, Bik did not alter nerve conduction velocity (NCV) of tail sensory and tail motor distal latency motor. While we found that hindpaw cutaneous innervations, protein gene produce (PGP9.5) positive nociceptor which mediated acute pain were degenerated and growth associated protein (GAP43) positive nociceptor which mediates chronic pain were sprouted. This indicates that Bik selectively caused pathological change in nociceptor instead in tail peripheral nerves trunk, causing treated mice developed dying back sensory neuropathy. Thus, we conclude that Bik is potentially an ART algogen, contributing to HIV-PAIN and causing HIV-SN. Further study will focus on the explore the nociceptive mechanism and find mechanism based analgesic approaches for HIV-PAIN.

Disclosures: A. Pal: None. **Y. zhou:** None. **H. Li:** None. **D. Ajasin:** None. **B. Gong:** None. **S. Valdebenito-Silva:** None. **E. Eugenin:** None. **S. Yuan:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.09/U29

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

Support: NIH Grant K01NS129895

Title: G1 mediates HIV- induced mitochondrial dysfunction and oxidative stress

Authors: R. COOK[1], J. DE VASTEY[3], E. OMOGBAI[4], *K. S. WILLIAMS[2];
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Abstract: Approximately 1.1 million Americans are affected by Human Immunodeficiency Virus (HIV) in the United States. Due to the success of anti-retroviral treatments (ART), the median age of people living with HIV are 50 years old. Despite the success of ART increasing

the life expectancy and overall quality of life, many living with HIV still suffer from co-morbidities, including neurological complications and stress- related disorders. In fact, 30-50% of people living with HIV experience an umbrella of neurocognitive impairments are referred to as HIV-associated neurocognitive disorders (HAND). HAND is predicted to increase with aging; therefore, more targeted therapeutics approaches are needed. Previous studies have shown that natural estrogens are neuroprotective and can inhibit HIV infection in primary macrophages and peripheral blood mononuclear cells via classical estrogen receptors. However, the role of the non-classical estrogen receptor, GPER, in HIV induced neuroinflammation is unknown. GPER has been shown to have positive effects on mitochondrial health and oxidative stress. Therefore, we hypothesize that activation of GPER via a specific GPER agonist, G1 will reduce HIV-induced oxidative stress and neuroinflammation by increasing mitochondrial integrity. To test this, we utilized a dual cell *in vitro* model consisting of human monocyte-derived macrophages (MDMs) and rat cortical neurons. We found that HIV leads to increased neurotoxicity, reduced antioxidant expression of HO-1, HO-2, and SOD. Mitochondrial protein, SIRT3 was reduced and fragmented mitochondrial was seen during HIV exposure in human monocyte derived macrophages. Pretreatment with G1 prior to HIV exposure reduced neurotoxicity and increased SIRT3 and antioxidant protein expression in a GPER dependent manner. Therefore, GPER activation may reduce HIV induced mitochondrial changes and serve as a potential novel therapeutic approach for HAND.

Disclosures: R. Cook: None. **J. de Vastey:** None. **E. Omogbai:** None. **K.S. Williams:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.10/Web Only

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

Support: NIH grant R01 DA057197
NIH grant R01 DA044552-03S1
NIH grant NS060632
NIH grant MH122241

Title: Effects of combined antagonism of calcium channel/NMDAR overactivation and cART on mPFC neuron dysfunction induced by Coc self-administration and neuroHIV in rats

Authors: *L. CHEN, D. IMERI, L. AL-HARTHI, X.-T. HU;
Rush Univ. Med. Ctr., Chicago, IL

Abstract: Cocaine (Coc) is a highly addictive and widely abused psychostimulant. Chronic exposure to Coc or HIV induces neuron hyperactivity in the medial prefrontal cortex (mPFC, a critical regulator of cognition and addiction); and that is worsened when they are comorbid. Combined antiretroviral therapy (cART) suppresses active HIV replication, prolonging life of

HIV^+ individuals, but the prevalence of HIV-associated neurocognitive disorders (HAND, a.k.a. neuroAIDS/HIV) still occurs in ~50% of people living with HIV. Our previous study and research of others indicate that, besides therapeutic effects, chronic Triumeq (a first-line cART regimen) also induces cortical neuron hyperactivity and neurotoxicity, which could worsen neuroHIV-induced neurotoxicity. Our published work also revealed that Coc, HIV, or even cART independently induces cortical neuron dysfunction, resulting from the alterations in their excitability mediated by overactive membrane Ca^{2+} channels (e.g., the L-channel). Moreover, we also demonstrated that combinedly targeting overactive L-channels/NMDARs abolished neuroHIV-induced cortical neuron hyperactivity and Ca^{2+} dyshomeostasis. However, whether combined blockade of overactive L-channels/NMDARs eliminates the joint deleterious effects of Coc self-administration (Coc-SA) and neuroHIV, with or without cART, on cortical neurons, is still unknown. To fill this knowledge gap, we start to explore the therapeutic potential of combined blockade of L-channel/NMDAR overactivation in the Coc-SA/neuroHIV comorbidity, in combination with chronic cART treatment, modeled in HIV-1 transgenic (Tg) rats. Age-matched F344 non-Tg rats are used as control. Electrophysiology (whole-cell patch-clamping) approaches are used to assess functional activity of mPFC pyramidal neurons in brain slices from Coc-SA HIV-1 transgenic (HIV-Tg) rats at age of ~6-month. Rats will also receive daily repetitive s.c. injections of Triumeq and/or selective L-channel and NMDAR blockers (diltiazem and memantine, respectively) for 28 days (d). On d15-19, and d22-26, rats will perform Coc-SA for 2 hours/d. After 3-10d of withdrawal from the last SA, rats will be killed and prepared for defining the mechanism by which cortical neuron excitability is altered by Coc-SA, neuroHIV, cART, and/or blockade of L-channel/NMDAR overactivation. Our pilot study suggests that Coc-induced neuronal hyperactivity is worsened by chronic cART, and *vice versa*.

Disclosures: L. Chen: None. **D. Imeri:** None. **L. Al-Harthi:** None. **X. Hu:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.11/U30

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

Support: R01NS138288
U24MH137478

Title: Sensory Neuron Hyperexcitability during Latent Trigeminal HSV-1 Infection

Authors: J. AI, J. LIU, C. SHIN, A. VENTRONE, ***V. HSIA**;
Univ. of Maryland Eastern Shore, Princess Anne, MD

Abstract: Previously, we demonstrated that herpes simplex virus 1 (HSV-1) establishes a quiescent, latency-like state in differentiated human dorsal root ganglion (HD10.6) neuronal cells characterized by a void of viral replication, significant hyperexcitability, and elevated voltage-

gated sodium channel density. In this study, we validated these findings in vivo using fiber photometry in a mouse model expressing GCaMP6s in the trigeminal ganglia (TG). Following corneal HSV-1 infection, basal spontaneous neuronal activity ceased at 1-day post-infection (dpi) but recovered by 28 dpi, displaying marked hyperexcitability that confirms our in vitro observations. Notably, a distinct subset of animals ("Fast Recoverers") achieved rapid functional recovery by 14 dpi. Transcriptional profiling of the HSV-1 acute gene ICP0 revealed identical lytic gene-silencing kinetics between both groups, aligning with the baseline resolution curve. Remarkably, analysis of the HSV-1 latency-associated transcript (LAT) demonstrated that Fast Recoverers possessed a 13.9-fold increase in LAT abundance at 14 dpi compared to non-recovered animals. Furthermore, the absolute LAT transcript pool in Fast Recoverers at 14 dpi was statistically equivalent to levels typically observed during established latency at 28 dpi. Collectively, these findings demonstrate that murine TG sensory neurons undergo a highly coordinated lytic-to-latent transcriptional transition defined by early lytic silencing and sustained, high-level LAT expression as neurons shift toward a latency-supportive state. Critically, the Fast Recoverer subpopulation truncates the functional recovery timeline by 50% while compressing the standard 28-day LAT accumulation window into just 14 days. These data strongly suggest that the rapid accumulation of this viral non-coding RNA, paired with host adaptive responses, acts as a critical physiological driver of latent-phase neuronal hyperexcitability.

Disclosures: J. Ai: None. **J. Liu:** None. **C. Shin:** None. **A. Ventrone:** None. **V. Hsia:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.12/U31

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

Support: NIH Grant R01DA051893
NIH Grant R01DA056876
NIH Grant R01MH136852
NIH Grant R01MH139446-01A1

Title: Modeling and Eradicating Latent HIV Infection in Human iPSC-derived Vascularized Microglia-Containing Cerebral Organoid (vMCO)

Authors: *I. SISTO[1], A. BALOCH[2], D. ZHANG[3], R. HOSSAIN[4], Y. TANG[8], X. YUAN[5], X. WANG[9], D. JAIJYAN[6], J. XU[2], B. ANGELES[2], W.-Z. HO[10], G. JIANG[8], W. HU[7];
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Abstract: NeuroHIV remains a major barrier to a complete HIV cure because the central nervous system (CNS) harbors persistent viral reservoirs. Within the CNS, resident microglia serve as the primary site for long-term viral residency and persistence. While antiretroviral therapy (ART) effectively suppresses active replication despite restricted penetration across the blood-brain barrier (BBB), developing an in vitro model that successfully recapitulates and validates inducible latency has remained elusive. Here, we present a vascularized, microglia-containing cerebral organoid (vMCO) platform that mimics human brain vasculature to sustain robust microglial integration and enable long-term viral persistence studies. To model physiological reservoirs, vMCOs were infected with the HIV-1 clone LG29-MG, derived from microglia isolated from the brains of people with HIV (PWH) postmortem. The vMCO model supported active HIV-1 replication, which was efficiently suppressed by ART to establish a stable, latent infection. Crucially, viral rebound following ART interruption and a robust viral expression spike induced by the latency-reversing agent JQ1 confirmed a functional, inducible, and latently infected proviral reservoir. To evaluate curative interventions, we deployed an AAV-DJ8-delivered saCas9 system with multiplex sgRNAs targeting the HIV LTR and gag. In the absence of ART, CRISPR knockout blocked >90% of HIV-1 replication. Furthermore, gene editing completely prevented viral rebound following ART cessation and abrogated JQ1-mediated latency reversal, verifying the effectiveness of CRISPR-driven proviral eradication. Collectively, this vMCO platform represents the first human brain model capturing the full spectrum of persistent NeuroHIV dynamics—including active infection, latency establishment, reversal, and therapeutic eradication. These findings provide a highly translationally relevant platform for investigating NeuroHIV neuropathogenesis, substance use disorder comorbidities, and CNS-targeted curative strategies

Disclosures: I. Sisto: None. **A. Baloch:** None. **D. Zhang:** None. **R. Hossain:** None. **Y. Tang:** None. **X. Yuan:** None. **X. wang:** None. **D. Jaijyan:** None. **J. Xu:** None. **B. Angeles:** None. **W. Ho:** None. **G. Jiang:** None. **W. Hu:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.13/U32

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

Support: MR/X032019/1

Title: Neuroimmune, metabolic, and fluid dysregulation during cryptococcal infection of the brain

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Abstract: Cryptococcal meningitis is a life-threatening fungal infection of the central nervous system and a leading cause of neurological disability and death among immunocompromised individuals. Despite its clinical importance, the mechanisms driving brain injury during infection remain poorly understood. Here, we employed a multimodal approach integrating multi-omics analyses, multiplex cytokine profiling, advanced bioimaging, and glymphatic assessments to define the neurobiological pathways underlying cryptococcal brain injury.
Our findings demonstrate that Cryptococcus is a highly neurotropic pathogen that invades the brain through the vascular system. During early infection, fungal cells are phagocytosed by microglia, which paradoxically exhibit limited transcriptional remodeling and minimal cytokine production despite evidence of fungal recognition. In contrast, astrocytes and neurons undergo extensive transcriptional reprogramming, revealing widespread alterations in inflammatory, immunometabolic, and cellular stress pathways. As infection progresses, a dysregulated neuroinflammatory state emerges, characterized by increased chemokine production, recruitment of peripheral immune cells, and progressive tissue injury.
Three-dimensional imaging revealed progressive perivascular accumulation of fungal cells accompanied by enlargement of perivascular spaces. Using intracisternal tracer studies, we further demonstrate impaired cerebrospinal fluid transport and reduced glymphatic influx during infection. These alterations provide a potential mechanistic basis for the development of raised intracranial pressure and hydrocephalus, major contributors to mortality in cryptococcal meningitis.
Collectively, our findings redefine cryptococcal brain injury as a multifactorial process driven by interconnected neuroimmune, metabolic, and neurofluid disturbances. Rather than arising solely from inflammatory pathology, cryptococcal neuropathology emerges from the convergence of multiple dysregulated biological systems, revealing previously unrecognized mechanisms of neurological injury during fungal infection of the brain

Disclosures: R. Dangarembizi: None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.14/V1

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

Support: NIH Grant R33DA058501
NIH Grant R01DA057337
NIH Grant K01MH132466
NIH Grant F30DA064444

Title: The effects of dopaminergic signaling on HIV infection and neuroinflammation in human neural organoids

Authors: *Y. AGARWAL[1], A. MODICA[1], J. MONTILLA[1], S. MATT[3], T. KIST[1], V. C. OGBOLU[5], M. DANIALI[1], L. QIANG[4], H. S. FOX[6], P. J. GASKILL[2];
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Abstract: HIV-associated neurologic complications affect nearly half of people with HIV and are driven in part by persistent viral reservoirs in microglia and macrophages. Methamphetamine (METH) use is more prevalent among people with HIV and is associated with increased viral burden, though the mechanisms underlying this interaction remain unclear. We previously showed that dopamine enhances HIV replication and cytokine release in myeloid cells, suggesting that METH-induced dopaminergic signaling may exacerbate HIV neuropathogenesis. Here, we developed human iPSC-derived cortical (low dopaminergic tone) and midbrain (high dopaminergic tone) organoids with co-cultured microglia (iMg) to model region-specific neuroimmune interactions. Organoid identity and iMg incorporation were validated by qPCR, immunostaining, and transcriptomic profiling. METH-induced dopamine release and neuronal activity were assessed using live-cell imaging and multi-electrode arrays. Organoids were infected with CCR5-tropic HIV +/- chronic METH treatment from 5 to 20 days-post-inoculation (DPI; n=3-7 per group). HIV viral capsid (p24Gag) and cytokine secretion were quantified in culture supernatants using AlphaLISA assays. Measurements of p24Gag secretion revealed that HIV replication required iMg integration, and HIV p24Gag localized exclusively to iMg by immunostaining. METH increased HIV replication in midbrain organoids (~3.5-fold) by 14 DPI but not cortical organoids. Consistent with a dopamine-dependent mechanism, apomorphine increased viral replication in cortical organoids (~4-fold). HIV infection induced CCL2 secretion in a microglia-dependent manner and was attenuated by antiretroviral treatment. Follow-up studies (n=4 per group) using A1-inducing cytokines (TNFα, IL-1α, and C1q) showed that activated astrocytes released CCL2 ($p<0.01$) in microglia-deficient midbrain organoids. However, CCL2 secretion in response to LPS ($p<0.05$) or METH ($p<0.05$) required microglia integration, highlighting dynamic intercellular crosstalk between dopaminergic neurons, microglia, and astrocytes. Our findings show that regional dopaminergic tone modulates microglial HIV infection and neuroinflammatory signaling in a human organoid model, with CCL2 as a possible feed-forward myeloid recruitment pathway. This work implicates dopamine as an intermediate link between METH exposure and accelerated HIV neuropathogenesis.

Disclosures: Y. Agarwal: None. **A. Modica:** None. **J. Montilla:** None. **S. Matt:** None. **T. Kist:** None. **V.C. Ogbolu:** None. **M. Daniali:** None. **L. Qiang:** None. **H.S. Fox:** None. **P.J. Gaskill:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.15/V2

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

Support: NIH R01MH108466
NIH R56NS124422
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NIH R56AG089864
NIH R01AG089864-01A1

Title: Cerebellar volume loss in adults with chronic HIV disease

Authors: *G. HANLY, S. QI, P. THOMAS, H. LEE, X. JIANG;
Dept. of Neurosci., Georgetown Univ., Washington, DC

Abstract: In the USA, the median age of people with HIV (PWH) is now over 50 years old. This rapidly aging population emphasizes the need for research to understand the long-term impact of chronic HIV-disease on brain structure and function, especially in the context of transitioning from middle age to geriatric age. By utilizing high-resolution T1-weighted MRI images from 101 PWH (41-70 years old (56.3±6.6), 25.7% female at birth, 64.4% African Americans, 14.4±3.0 years of education, 80.6% with undetectable viral load, 25.1±9.2 years disease duration) and 40 healthy controls (41-70 years old (54.7±7.2), 30.0% female at birth, 60.0% African Americans, 14.5±2.8 years of education), we investigated the impact of HIV disease on cortical, subcortical, and cerebellar gray matter volume (GMv) and white matter volume (WMv). 76 PWH completed a baseline visit (V1) and a follow-up visit (V2, approximately two years after V1), while all controls and the other 25 PWH only completed V1. Thus, the data was divided into two separate sets based on the availability of V2 data: a cross-sectional data set with V1 data from all 40 controls and 25 PWH who did not participate in V2, and a longitudinal data set with V1 and V2 data from 76 PWH. MRI images were segmented with FreeSurfer (version 8.2.0), using the default pipeline and parameters. Hemispheric volumes were combined, and demographics and intracranial volume were included as covariates in all analyses. False discovery rate (FDR) correction was used for multiple comparisons. ANCOVAs with the cross-sectional data set revealed that compared to healthy controls, PWH had lower cerebellar GMv (q<.05), cerebellar WMv (q <.01), and cortical GMv (q <.05), but not subcortical GMv (q >.1) or cortical+subcortical WMv (q >.7). Using the longitudinal data, linear mixed-effects model analyses were conducted for cortical GMv, cerebellar GMv, and cerebellar WMv. Older age was associated with lower cortical and cerebellar GMv, and less educational attainment was associated with lower cerebellar GMv and WMv. Importantly, longer disease duration was associated with lower cerebellar WMv. However, there was no significant change between V1 and V2. These findings support that brain injury is still highly prevalent in PWH in the era of successful antiretroviral therapies, including prominent cerebellar volume loss, which may contribute to high prevalence of motor, cognitive, and emotion impairment in PWH. Future longitudinal studies with longer duration that focus on the critical transitioning period from middle- to geriatric- age are warranted, especially given the negative impact of disease duration on the brain structure.

Disclosures: G. Hanly: None. **S. Qi:** None. **P. Thomas:** None. **H. Lee:** None. **X. Jiang:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.16/V3

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

Support: NIH/NIDA R01DA055568.

Title: Oral Taurine Administration Mitigates Taurine Dysregulation & Impairment of Memory and Mood in a Mouse Model of Comorbid HIV-Tat/Opioid Use Disorder

Authors: *K. A. GEORGE[1], R. SHINOUCHI[1], S. EANS[1], S. THANGAVEL[2], M. J. KAUFMAN[3], J. P. MCLAUGHLIN[1];
[1]Cell. & Systems Pharmacol., Univ. of Florida, Gainesville, FL; [2]Pharmaceut. Sci., Texas A& M University, Col. of Pharm., College Station, TX; [3]McLean Hosp, Belmont, MA

Abstract: Comorbid opioid abuse and HIV is a highly prevalent, yet understudied and undertreated disorder, given many people living with this disorder are over 50 years old. Blood and brain taurine (Tau) levels are dysregulated by opioids and HIV exposure. Concurrent opioid use and HIV are thought to synergistically amplify mitochondrial impairments, enabling or perpetuating substance abuse and mood and cognitive dysfunction. We tested whether exposures to morphine and **HIV Transactivator of Transcription (Tat) protein impair memory**, **potentiate depression-like and morphine conditioned place preference behaviors**, **alters Tau transporter (SLC6A6) expression, and whether oral Tau mitigates the effects of morphine and Tat exposure**. Young adult iTat transgenic mice, in which doxycycline (Dox) induces Tat expression, were dosed (i.p.) for 7 days with saline, Dox (100 mg/kg/day), or Dox+morphine (30 mg/kg, BID); or these treatments + prophylactic Tau (500 mg/kg/day, p.o.). One Dox+morphine group was tested after Tau was given once after those treatments (day 8). Mice then underwent Novel Object Recognition (NOR), Tail Suspension Test (TST), and Conditioned Place Preference (CPP) testing, and brains were harvested for Western Blot analysis. Exposure to Tat alone or with morphine significantly reduced blood Tau levels, impaired Phase 3 NOR (memory; $(F(3,88)=7.59, P=0.0001)$, attenuated by Tau prophylactic treatment, and prolonged time spent immobile in the TST (depression-like behavior) that was attenuated by 1 or 7 days oral Tau ($F(3,84)=46.0, P<0.0001$). In Western blot analysis of isolated frontal cortex, Tat and morphine exposure both activated glycogen synthase kinase 3β (GSK3β) and reduced peroxisome proliferator-activated receptor gamma coactivator-1α (PGC1α) thought to impair mitochondrial function. Notably, SLC6A6 expression was dysregulated by Tat and MOR, but upregulated by 7 days of oral Tau treatment ($F (3,8) =114.3, P<0.0001$). Collectively, this data shows that concurrent Tat protein and morphine exposures substantially impaired memory, mood, and SLC6A6 expression, which was blunted by oral supplementation of Tau,

highlighting therapeutic benefits to treat people with comorbid opioid use disorder/HIV.
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Disclosures: K.A. George: None. **R. Shinouchi:** None. **S. Eans:** None. **S. Thangavel:** None. **M.J. Kaufman:** None. **J.P. McLaughlin:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.17/V4

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

Support: NIH Grant 5R01NS135166-03

Title: ATRX drives early HSV-1 genome silencing to establish latency in peripheral neurons

Authors: *Z. E. REICH[1], A. L. WHITFORD[2], A. R. CLIFFE[1];
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Abstract: Herpes simplex virus-1 (HSV-1) infects over 60% of the global population with latent infections in peripheral neurons. No therapeutics currently exist that can treat or remove HSV-1 from neurons. During latency, the viral genome is silenced through heterochromatinization. Certain stresses can lead to reactivation, and potential viral spread into the brain, causing deadly encephalitis. Determining the drivers of initial viral genome silencing is essential to preventing latency establishment and reducing the reactivation events that cause disease. De novo chromatin assembly to silence the HSV-1 genome is not yet understood. ATRX (Alpha-Thalassemia/Mental Retardation X-linked) is a chromatin remodeler that is a great candidate for modulating HSV-1 latency establishment as it deposits the histone variant H3.3, represses repetitive genomic elements, and resolves G-quadruplex (G4) secondary DNA structures. Previously, our lab demonstrated that ATRX promotes a deeper form of viral silencing and restricts HSV-1 reactivation (Whitford et al., 2025). Here, we investigate whether ATRX acts early during infection to establish latency. To test this, we use ATRX shRNA knockdown (KD) in human HD10.6 neurons and conditional ATRX knockout (cKO) in superior cervical ganglia (SCGs) dissected from ATRX-floxed mice (P0-2, mixed sex). For HSV-1 infection, we can observe infection at a single-cell level using our gH-null/US11-GFP virus (Stayput-GFP). Viral gene expression was quantified by single-genome immunofluorescence imaging across multiple timepoints. Pre-infection ATRX knockdown in SCGs significantly disrupted latency establishment over 30 days post-infection. At 24 hours post-infection, both KD and cKO showed significantly elevated viral gene expression and a greater proportion of actively infected neurons—indicative of ATRX promoting heterochromatinization of the viral genome near nuclear entry by the viral genome. Together, these findings establish ATRX as critical for HSV-1 latency establishment in peripheral neurons and a potential therapeutic target for preventing latency. Understanding how ATRX assembles repressive chromatin de novo on a foreign viral

genome has broader implications for developmental neuroscience, neuroepigenetics, and brain cancer biology.

Disclosures: Z.E. Reich: None. **A.L. Whitford:** None. **A.R. Cliffe:** None.

Poster

PSTR092: Viral and Infectious Mechanisms of Neuroinflammation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR092.18/V5

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

Title: Integrated single-nucleus reference of neuroimmune and vascular cell states across addiction-relevant human brain regions

Authors: *A. DOMINGUEZ[1], K. J. BENJAMIN[2];
[1]Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL; [2]Psychiatry & Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Integrated single-nucleus reference of neuroimmune and vascular cell states acrossaddiction-relevant human brain regions

Abstract
Opioid use disorder (OUD) remains a major public health crisis and is frequently complicated by HIV, a comorbidity in which opioid exposure, viral proteins, inflammation, and vascular dysfunction may converge on the blood-brain barrier. The neurovascular unit (NVU), composed of endothelial cells, pericytes, vascular smooth muscle cells (vSMC), and astrocytes, and other supporting cell types, is central to blood-brain barrier maintenance and cerebral blood-flow regulation. However, the baseline organization of glial, immune, and vascular-associated cell states across addiction-relevant human brain circuits remains poorly defined. Establishing this reference is a necessary first step toward determining how OUD, HIV, and their comorbidity remodel neuroimmune and neurovascular programs. Here, we establish a region-aware single-nucleus reference across four addiction-relevant human brain regions: dorsolateral prefrontal cortex, nucleus accumbens, insula, and amygdala. We integrated five publicly available single-nucleus RNA-seq datasets anchored on the Human Brain Cell Atlas and complemented by reward-circuit, cortical, and neurotypical control resources. After source- and region-specific quality control, we recovered 70,279 high-quality glial, immune, and vascular-associated nuclei. Donor-aware latent-variable integration followed by consensus clustering resolved 21 transcriptionally distinct cell states with cross-donor support, including astrocyte, microglial, monocyte/macrophage, T/NK, endothelial, and pericyte/vSMC populations. Module-score profiling across six neuroimmune gene programs - CNS microglia homeostatic, activated myeloid, peripheral monocyte, reactive astrocyte, endothelial, and mural/pericyte - demonstrated clear biological separation of resident, activated, peripheral-like, astrocytic, and vascular-associated states. Homeostatic microglia and activated microglia partition along the CNS-

resident and activated-myeloid axes, while monocyte/macrophage state separated toward the peripheral monocyte axis. Astrocyte states captured a reactive-to-quiescent continuum, and vascular states were recovered with cross-cohort donor support. Together, these define a stable reference vocabulary for quantifying neuroimmune and neurovascular remodeling in OUD, HIV, and neuro-HIV comorbidity.

Disclosures: A. Dominguez: None. **K.J. Benjamin:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.01/V6

Topic: D.03. Stroke

Support: This research was supported by a National Research Foundation (NRF) of Korea grant funded by the Korean government (NRF-2023R1A2C2006414 and RS-2025-00558588).

Title: Macromolecular drug delivery using magnetic stimulation for stroke treatment

Authors: *K. CHOI, J. KIM;
Chonnam Natl. Univ. Hosp., Gwangju, Korea, Republic of

Abstract: While Brain-Derived Neurotrophic Factor (BDNF) holds profound neurorestorative potential for stroke recovery, its clinical application remains severely restricted by poor blood-brain barrier (BBB) penetrance. Here, we investigated a novel, non-invasive platform utilizing focused magnetic stimulation (MagStim) to transiently modulate the BBB and facilitate macromolecular BDNF delivery. Using a rat model of transient middle cerebral artery occlusion (tMCAO), treatments were administered during the chronic recovery phase (14 days post-onset). Experimental cohorts included Sham, tMCAO control, systemic BDNF alone, and MagStim + BDNF combination. In vivo imaging and molecular analyses (IVIS, ELISA) revealed that MagStim significantly amplified ipsilesional BDNF accumulation compared to BDNF administration alone ($p = 0.011$). Crucially, the MagStim + BDNF paradigm was the sole intervention to yield a robust reduction in structural infarct volume (MRI, $p = 0.043$). Although basal neurological deficits improved across treatment groups, only the combinatorial approach drove highly significant motor recovery ($p < 0.001$) without causing sustained BBB disruption. Mechanistically, MagStim + BDNF therapy suppressed peri-infarct apoptosis and pro-inflammatory cytokine surges, preserved tight junction integrity, and robustly upregulated neurogenesis markers. These findings highlight magnetically controlled BBB modulation as a highly effective, translational strategy to overcome macromolecular delivery bottlenecks, maximizing the therapeutic efficacy of neurotrophin-based stroke treatments.

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

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.02/V7

Topic: D.03. Stroke

Support: Swedish Research Council
Swedish Brain Research Foundation

Title: Intranasal treatment with synthetic C3a analogue improves recovery after ischemic stroke

Authors: M. MODE, A. PEKNY, A. STOKOWSKA, U. WILHELMSSON, M. PEKNY, *M. PEKNA;
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Abstract: Stroke is a devastating disease that affects around 12 million people annually and despite advances in the acute care, 50% of the survivors live with permanent disability. Despite its massive impact on health and society, treatment options beyond the acute phase after stroke are limited to rehabilitative interventions and secondary prevention. Addressing this issue, we previously demonstrated that daily intranasal administration of C3a, a 77 amino acid peptide generated by proteolytic activation of the third complement component and purified from human serum, initiated one week after stroke, enhances functional recovery in mice. Furthermore, we showed that C3a treatment is associated with increased neural plasticity and modulation of reactive gliosis in the peri-infarct region (Stokowska et al, Brain, 2017; Stokowska et al, J Clin Invest, 2023). Here we tested whether a synthetic C3a analogue would reproduce the beneficial effects observed after treatment with the native C3a. Seven days after induction of ischemic stroke in the motor cortex, mice were randomised to receive the C3a analogue or vehicle via daily intranasal administration for three weeks. Motor function was assessed by grid walk and cylinder tests prior to stroke induction, prior to treatment initiation, after one week of treatment and after the last treatment. We found that the C3a analogue-treated mice showed better improvement of motor function than mice treated with vehicle. The treatment groups did not differ in infarct volume. We conclude that the efficacy and potency of the C3a analogue in enhancing motor function recovery after ischemic stroke are similar to those of native C3a.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.03/V8

Topic: D.03. Stroke

Support: Swedish Research Council
Swedish Brain Research Foundation

Title: Intranasal treatment with complement C3a enhances functional recovery after intracerebral hemorrhage

Authors: M. PEKNA, M. MODE, M. MICHALOWSKA, A. PEKNY, A. ARNMARK, A. STOKOWSKA, U. WILHELMSSON, *M. PEKNY;
Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Intracerebral hemorrhage (ICH) affects around 3.4 million people each year with global prevalence of almost 21 million. In over 30% of cases, ICH leads to death within 90 days and many ICH survivors live with long-term neurological impairment, underscoring the need for strategies that promote long-term functional recovery. C3a receptor (C3aR) is a G-protein coupled receptor expressed by astrocytes, microglia, neurons and neural stem cells. After ischemic stroke, C3aR stimulates neural plasticity in the peri-infarct region. In a recent multicenter study in mice, we showed that intranasal C3a accelerated recovery of motor function in the post-acute phase after ischemic stroke. These results identified C3a as an attractive translational strategy to promote long-term recovery after ischemic stroke. Compared to ischemic stroke, ICH is associated with higher early morbidity and mortality, but - as in ischemic stroke - ICH survivors also show some functional improvement during the later phase. The aim of this study was to determine the effects of intranasal C3a treatment on functional recovery after ICH induced in mice by collagenase injection into the striatum. At the end of the 3-week-long daily treatment period starting 7 days after ICH induction as well as 4 weeks after treatment cessation, we found improved motor function in mice treated with C3a, but not in mice that received vehicle. The C3a- and vehicle-treated mice did not differ in astrocyte reactivity, the density of microglia or iron storage in the lesioned striatum. We conclude that post-acute intranasal treatment with C3a is a promising and clinically feasible strategy to improve outcome after ICH.

Disclosures: M. Pekna: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovera AB. **M. Mode:** None. **M. Michalowska:** None. **A. Pekny:** None. **A. Arnmark:** None. **A. Stokowska:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovera AB. **U. Wilhelmsson:** None. **M. Pekny:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurorecovera AB.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.04/Web Only

Topic: D.03. Stroke

Support: NIH NINDS R01 NS106441

Title: Effects of a TREM2 Agonist Antibody in a Mouse Model of Distal Middle Cerebral Artery Occlusion

Authors: Z. ZHENG[1], **L. ZHENG**[2], J. SHI[3], R. KACIMI[4], *M. A. YENARI[5];
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Abstract: Stroke remains a leading cause of death and long-term disability worldwide with few proven treatments. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), an immune receptor found on microglia, is a potential therapeutic target for stroke recovery, as the activation of TREM2 leads to phagocytosis and modulates post-stroke inflammation. We previously showed that TREM2 deficient mice had worse outcomes compared to mice with intact TREM2, and this was associated with increased pro-inflammatory markers and almost complete inhibition of phagocytosis. Here, we utilized a murine stroke model to test whether a TREM2 agonist antibody (TREM2ab) might lead to improved outcomes. Male (n=6/group) and female (n=10/group) mice ~3 mos of age underwent permanent distal middle cerebral artery occlusion (dMCAO). Mice received 80mg/kg of TREM2ab, while the control group received an isotype control (CONab). The first dose was given immediately after dMCAO, while a second was given 3 d later. Sham groups (n=11) were studied for comparison. Neurological deficits were assessed at baseline, then 3, 7, & 14 d post dMCAO. Behavioral assays included: Bederson score, elevated body swing test (EBST), and adhesive removal test. Brains were collected at 14 d, and infarct sizes were evaluated using hematoxylin and eosin (H&E) staining. ANOVA was used to analyze the infarct sizes between the groups, and two-way ANOVA was used to observe body swing and adhesive removal time. In both male and female cohorts, TREM2ab failed to show differences in lesion size or behavioral outcomes. Infarct sizes in male mice (n=6/group) were 14% ±0.1 vs 15% ±0.07, and in female mice (n=7/group) 18.4% ± 7% vs 17% ± 7% (TREM2ab vs CONab respectively; P=NS). 10 female mice/group were available for behavioral assays, but there were no differences between the dMCAO groups, although dMCAO groups performed worse than shams. The underlying reasons for a lack of effect by TREM2 stimulating antibodies are unclear. While these antibodies do penetrate into the brain, it is possible that in our stroke model, TREM2 is already maximally stimulated, with little window for further improvement. Thus, TREM2 may be a therapeutic target in selected stroke subpopulations, but not in the one modeled here.

Disclosures: Z. Zheng: None. **L. Zheng:** None. **J. Shi:** None. **R. Kacimi:** None. **M.A. Yenari:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.05/Web Only

Topic: D.03. Stroke

Support: Fundación IMSS, from Instituto Mexicano del Seguro Social, with the grant number: R-2024-1305-05, 2025-15-2.

Title: Acute 7,8-Dihydroxyflavone Induces Early Reduction of Infarct Size and Astrogliosis in Rats with Permanent Middle Cerebral Artery Occlusion

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Abstract: The neurotrophin receptor TrkB influences neuronal survival, synaptic stability, and plasticity, making it a promising target for neuroprotection after ischemic stroke. 7,8-Dihydroxyflavone (7,8-DHF) is a small-molecule TrkB agonist that has shown neuroprotective effects in preclinical models. However, its immediate effects on early neurobiological and cognitive outcomes post-stroke are not well understood.Male Sprague-Dawley rats (n=36) underwent permanent middle cerebral artery occlusion (pMCAO) or sham surgery and received a single intraperitoneal dose of 7,8-DHF (5 mg/kg) or saline one hour after surgery. Recognition memory was tested 24 hours later using the novel object recognition (NOR) task. Brains were analyzed for CA1 pyramidal neuron dendritic structure (Golgi-Sholl analysis), and GFAP presence. Acute 7,8-DHF did not restore recognition memory or significantly change CA1 pyramidal neuron morphology. Treated animals showed smaller infarcts and lower peri-infarct GFAP expression.A single dose of 7,8-DHF after pMCAO shows early effects that indicate reduced ischemic injury and astrocytic reactivity, with no effect on cognition or neuronal morphology.Longer treatment and assessment are needed to evaluate the full potential of 7,8-DHF for stroke recovery.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

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Program #/Poster #: PSTR093.06/V9

Topic: D.03. Stroke

Support: NIH 1R01NS138259
NIH R01NS142187

Title: Intranasal delivery of elovanoids precursors protects the brain after experimental ischemic stroke in rats

Authors: *L. S. BELAYEV[1], C. METON DE ALENCAR GADELHA VIEIRA[2], A. JACOTTE-SIMANCAS[1], J. JI[1], G. GULSEN[3], F. NOUIZI[3], A. OBENAUS[4], P. MUKHERJEE[1], N. G. BAZAN[1];
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Abstract: Ischemic stroke is a leading cause of death and disability. Previously, we demonstrated that the intranasal (IN) delivery of very long-chain polyunsaturated fatty acid Elovanoid precursors (FFA 32:6n-3 or 34:6n-3) protects the brain seven days after an experimental stroke. ELVs improved behavioral deficit, decreased T2WI lesion volume, and protected the blood-brain barrier. The purpose of this study was to determine the dose-response and therapeutic window in rats 14 days after stroke. Male SD rats were subjected to 2h of MCAo, a composite neurological battery (0 = normal and 12 = maximal deficit) was assessed on days 1, 2, 3, 7, and 14; then rats were perfused with 4% paraformaldehyde, their brains were removed, and *ex vivo* MRI analysis of lesion volumes was performed. Dose-response study: FFA (34:6 or 32:6) (5, 10, or 15 µg per nostril; totaling 10, 20, or 30 µg per animal) or vehicle, delivered IN at 1, 24, and 48 hours after the onset of MCAo. Therapeutic window study: FFA 34:6 (10µg per nostril; totaling 20µg per animal) was administered IN at 3, 4, 5, and 6 h after MCAo. Physiological variables were stable and showed no significant differences between groups. There were no adverse behavioral side effects observed after ELV administration in the present study. Dose-response: treatments with FFA-34:6 (20 and 30µg) improved total neurological scores on days 7 (25, 38%) and 14 (36, 49%), FFA-32:6 (10, 20 and 30µg) on day 7 (44, 49, 53%) and day 14 (44, 61, 61%, respectively), compared to vehicles. T2WI revealed that rats treated with vehicle had large cortical and subcortical infarctions. In contrast, both treatments reduced T2WI lesion volumes on day 14 compared to vehicles, which were primarily located in the subcortical areas. Therapeutic window: FFA-34:6 (10 and 30µg) reduced cortical T2WI lesion by 77 and 49% and FFA-32:6 (20 and 30µg) by 99 and 48% compared to vehicle. FFA-34:6 improved behavior on days 1, 7 and 14, when administered at 4h (by 23-30%), 5h (by 23-30%), 6h (by 40-44%), 7h (by 31-33%). Total lesion volume was reduced by FFA-34:6 at 6 and 7h by 51 and 43%, copared to vehicle. In conclusion, our results indicate that FFA 32:6 and 34:6 provide high-grade neurobehavioral recovery and decrease lesion volumes at considerably moderate doses when administered up to 7h after MCAo. The neuroprotection observed here for the post-ischemic brain offers the basis to explore therapeutic translational avenues for ischemic stroke.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.07/V10

Topic: D.03. Stroke

Title: Focused Ultrasound-Driven Blood-Brain Barrier Disruption for Targeted Microglial Modulation in Stroke Treatment

Authors: *S. CHOI[1,2], J. WU[4], H. PARK[5], H.-G. KO[3], J. KANG[5,7,6], H. SHIN[8], D. KIM[3,9]; [1]Med. Sci., Chungnam Natl. Univ., Daejeon, Korea, Republic of; [3]Dept. of Oral Anat. & Neurobio., [2]Kyung Hee Univ. Col. of Dent., Seoul, Korea, Republic of; [4]Dept. of Neurol., Southwest Hospital, Third Military Med. Univ., Chongqing, China; [5]Dept. of Med. Sci., [6]Brain Res. Inst., Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of; [7]Dept. of Pediatrics, Chungnam Natl. Univ. Hospital, Chungnam Natl. Univ. Col. of Med., Daejeon, Korea, Republic of; [8]Dept. of Biochemistry-Molecular Biol., Eulji Univ. Sch. of Med., Daejeon, Korea, Republic of; [9]Dept. of Neurosci., Kyung Hee Univ., Seoul, Korea, Republic of

Abstract: Background: The treatment of ischemic stroke remains challenging, particularly in addressing secondary damage beyond the initial stages. Emerging therapies focus on modulating brain inflammation by targeting microglial activation. However, non-invasive gene delivery systems targeting microglia are not yet fully developed. In this study, we propose a novel approach to mitigate stroke-induced damage using poly(lactic-*co*-glycolic acid) (PLGA) nanoparticles designed to target microglia by enhancing blood-brain barrier (BBB) permeability. We utilized ultrasound/microbubble (US/MB) technology to evaluate the efficacy of intracranial nanoparticle drug delivery in a photothrombotic ischemic stroke model. **Results:** The intravenous delivery of PLGA nanoparticles assisted by US/MB demonstrated a marked improvement in efficiency compared to conventional intravenous methods, approaching the effectiveness of the intrathecal route. Furthermore, nanoparticles loaded with miR146a-5p, a key regulator of microglial inflammatory responses, were delivered via the US/MB-assisted intravenous route. This method resulted in decreased expression of inflammatory factors, reduced infarct volume, and improved motor function in mice with photothrombotic ischemia. **Conclusions:** These results suggest that focused US/MB-mediated BBB disruption can enhance the targeted delivery of miR146a-5p-loaded nanoparticles to microglia, presenting a promising neuroprotective strategy for ischemic stroke treatment.
Keywords: Blood-brain barrier, Ischemic stroke, MiR146a-5p, Nanoparticle, Ultrasound

Disclosures: S. Choi: None. **J. Wu:** None. **H. Park:** None. **H. Ko:** None. **J. Kang:** None. **H. Shin:** None. **D. Kim:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.08/V11

Topic: D.03. Stroke

Title: Orphenadrine-Arbutin combination ameliorates ischemic stroke through modulation of the Nrf2/ HO-1/HIF-1α/TFAM signalling Axis

Authors: *P. BALHARA, S. SHARMA, N. VASUDEVA;
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Abstract: Ischemic stroke (IS) decreases blood flow to brain areas, causing oxidative stress that leads to biochemical, behavioural, molecular, and cellular damage. Current treatments are limited by a small therapeutic window, creating an urgent need for effective therapies to improve patient outcomes. This study examined the neuroprotective effects of the combination of orphenadrine (NMDA antagonist) and arbutin (phenolic glycoside), referred to as OR+AR, against ischemic brain injury by targeting the Nrf-2/HO-1/HIF-1α/TFAM pathway. Male Wistar rats underwent 90-minute MCAO surgery followed by reperfusion; the drugs were given intraperitoneally at 10 mg/kg and 25 mg/kg. Rats were then sacrificed at various time points (24 hours and 21 days post-stroke) for assessments of neurobehavioral deficits, infarct size, inflammation, mitochondrial dysfunction, gene expression, and tissue morphology. Results showed that OR+AR treatment notably enhanced neurological recovery, reduced infarct size and neuroinflammation, and improved mitochondrial health. It increased the expression of HIF-1α and TFAM genes, decreased caspase-3 activation and iNOS gene expression, and boosted antioxidant levels of Nrf-2/HO-1. Overall, the data suggest that the OR+AR combination provides superior neuroprotection by supporting mitochondrial and neural functions and promoting neuronal survival through modulation of the Nrf-2/HO-1/HIF-1/TFAM pathways, indicating its potential as a promising candidate for concomitant therapy in ischemic stroke.

Disclosures: P. Balhara: None. **S. Sharma:** None. **N. Vasudeva:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.09/V12

Topic: D.03. Stroke

Support: Brain Research Hub UNCW Translational Research Grant UNCW

Title: Post-stroke Pharmaceutical Intervention Using Glucagon-like Peptide 1 Analogue Conjugated with Cell-Penetrating Peptide

Authors: *M. E. LORANG[1], J. T. HOLSTEN[2], L. OYKHMAN[2], M. WELLS[1], J. LUDINGTON[1], K. QUANN[3], A. STANLEY[1], M. FACCONE[1], Q. MORGAN[5], B. READLING[1], Y. WANG[4], T. C. PETERSON[1];

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Abstract: Stroke is a leading cause of death and long-term disability worldwide, with ischemic stroke provoking a neuroinflammatory cascade that drives secondary injury and worsened outcomes. Microglia-derived TNF, IL-1α, and C1q are key drivers of this response, promoting neurotoxic astrocyte states and exacerbated tissue damage. We hypothesized that activation of Glucagon-like peptide-1 receptors (GLP-1R) with the agonist exendin-4 (Ex4) would directly block neurotoxic reactivity of astrocytes, attenuate downstream inflammatory injury, and improve stroke outcomes. GLP-1R agonists are limited by rapid clearance and poor blood-brain barrier (BBB) penetration. We designed three cell-penetrating peptide-conjugated Ex4 constructs (Ex4-CPP1, Ex4-CPP2, and Ex4-CPP3) capable of facilitating BBB transport and assessed their ability to enhance CNS delivery, receptor binding affinity, reduce infarct volume, modulate peri-infarct glial and immune cell responses, and improve functional recovery following stroke.GLP1R agonist binding activity was assessed using a cAMP assay in GLP1Roverexpressing HEK293 cells (N = 7–8). EC50/Emax values were: Ex4CPP1 (3.84 pM,100.2%), Ex4CPP2 (53.6 pM,99.5%), Ex4CPP3 (574 pM,99.7%), and Ex4 (2.82 pM,100%). CPP-conjugated Ex4 demonstrated preserved GLP-1R agonist activity comparable to Ex4.Photothrombotic stroke was induced in the motor cortex of C57BL/6 mice ($N = 108$; $n = 12$/group). Female mice received PBS, Ex4, Ex4-CPP1, Ex4-CPP2, or Ex4-CPP3. Males received all treatments except Ex4-CPP3. Treatments were administered 4 hours post-stroke and daily until sacrifice on day 11 post-stroke.Motor functional recovery was assessed using the Grid Walk, Rotating Beam, and Tapered Beam tasks at baseline days -2, -1, and 1, 3, 7, and 10 days post-stroke.Neuroinflammatory responses were assessed by quantifying infarct volume (NeuN) and peri-infarct macrophage/microglia (CD68) and astrocyte (GFAP) cell coverage.Our results demonstrated improved functional recovery with Ex4-CPP1 and Ex4-CPP2 compared to Ex4 ($p < .05$). In females, all Ex4-CPP constructs significantly reduced infarct volume and astrocyte coverage (all $p < .05$), while macrophage/microglia coverage was unchanged. In males, Ex4-CPP2 significantly reduced infarct volume ($p = .048$), while astrocyte and macrophage/microglia coverage was unchanged.This study is the first to show that CPP-conjugated GLP-1R agonists enhance therapeutic efficacy in an experimental stroke model. These findings suggest that CPP-mediated delivery may overcome limitations in systemic clearance, reducing neuroinflammation, and improving functional outcomes after stroke.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.10/V13

Topic: D.03. Stroke

Support: NIH/NIA grant #R01AG088518

Title: Oxytocin Modulates Sex-Specific Recovery Following Ischemic Stroke in Aged Mice

Authors: *S. KAPSE[1,2], V. VENNA[2], L. D. MCCULLOUGH[2];
[1]UT Hlth., Houston, TX; [2]Neurol., McGovern Med. Sch., Houston, TX

Abstract: Post-stroke depression (PSD) affects approximately one-third of stroke survivors and is a major determinant of long-term disability. PSD is driven by chronic neuroinflammation, HPA axis dysregulation, monoaminergic dysfunction, and disruption of corticolimbic circuits, processes exacerbated by aging. Oxytocin (OXT), a hypothalamic neuropeptide with neuroprotective and anti-inflammatory properties, is depleted following stroke in both patients and aged mice, whereas peri-infarct tissue exhibits increased OXTR expression 48 h post-ischemia (mRNA, $p<0.01$; protein, $p<0.05$), suggesting a therapeutically relevant oxytocinergic window. We hypothesized that exogenous OXT following stroke using transient middle cerebral artery occlusion (tMCAO) model would improve affective and social outcomes in aged mice through sex-dependent modulation of OXTR signaling. 18-months-old male and female C57BL/6 mice underwent tMCAO and received OXT or vehicle beginning 24 h post-stroke. Plasma and brain OXT were quantified by ELISA, and peri-infarct OXTR expression was assessed by RT-qPCR, Western blotting, and immunofluorescence. Behavioral outcomes were evaluated using the Tail Suspension Test (TST; day 14), Sucrose Splash Test (SST; day 21), and Three-Chamber Sociability Test (3-CST; day 51). Aging reduced OXTR protein expression relative to young animals. Following stroke, females exhibited increased peri-infarct OXTR mRNA despite reduced protein levels, suggesting sex-specific regulation of oxytocin signaling. OXT increased latency to first immobility in both sexes ($p<0.05$) and selectively reduced total immobility in males ($p<0.05$), in TST, consistent with antidepressant-like effects. OXT-treated females exhibited accelerated post-stroke body weight recovery, an effect absent in males. OXT also reduced latency to first groom in the SST and increased interaction frequency with a novel conspecific in females ($p<0.05$) in 3-CST. These findings identify the oxytocinergic system as an underappreciated regulator of post-stroke recovery in aging. Female-specific OXTR induction after ischemia, together with enhanced social and physiological recovery, suggests differential engagement of oxytocin signaling pathways between sexes. The selective antidepressant-like efficacy of OXT in males further highlights biological sex as a critical determinant of therapeutic responsiveness and supports OXT as a promising sex-informed treatment strategy for PSD.

Disclosures: S. Kapse: A. Employment/Salary (full or part-time):; UT Health. **V. Venna:** A. Employment/Salary (full or part-time):; UT Health. **L.D. McCullough:** A. Employment/Salary (full or part-time):; UT Health.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

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Program #/Poster #: PSTR093.11/V14

Topic: D.03. Stroke

Support: CONACYT Grant A1-S-21433

Title: S allylcysteine diminishes blood glucose and has a neuroprotective effect after ischemia and reperfusion injury in diabetic rats

Authors: *K. GRANDE LUNA[1], J. BELLO MARTINEZ[2], O. GRANADOS VEGA[3], T. PACHECO[4], S. BAUTISTA PÉREZ[5], C. A. SILVA-ISLAS[6], D. BARRERA-OVIEDO[3], M. MENES ARZATE[3], P. MALDONADO[7];
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Abstract: Cerebrovascular disease (CVD) accounts for at least half of the neurological disorders treated in general hospitals and is one of the leading causes of mortality and disability in Mexico. In addition, type 2 diabetes mellitus (T2DM) is the second leading cause of death and the primary cause of disability in the country, with a national prevalence of 18.3% according to ENSANUT 2022. Patients with T2DM of more than 10 years' duration have a threefold increased risk of developing ischemic CVD. Also, diabetic patients who suffer a stroke have a significantly worse prognosis, as diabetes is associated with a 56% higher mortality rate and 42% higher risk of recurrent ischemic stroke. Therefore, it is essential to develop experimental models of ischemic CVD that incorporate relevant comorbidities such as DM.S-allylcysteine (SAC) has demonstrated neuroprotective effects in cerebral ischemia/reperfusion (IR) models and hypoglycemic effects in diabetes models. However, the effect of SAC in diabetic animals subjected to cerebral IR has not been fully evaluated.Objective: To evaluate the effect of SAC in diabetic animals subjected to cerebral ischemia/reperfusion.Results: Administration of SAC in the DM+IR+SACpre and DM+IR+SACpost groups partially reduced capillary blood glucose levels compared to the DM+IR group; however, the greatest reduction was observed in the DM+IR+SACpre group. Additionally, diabetic animals that received SAC prior to IR (DM+IR+SACpre) exhibited fewer motor impairments than the DM+IR group, whereas those treated after IR (DM+IR+SACpost) did not show functional recovery. Finally, both the pre- and post-treatment groups exhibited a lower percentage of damaged cells than the DM+IR group.Conclusion: Diabetic animals that received SAC prior to IR (prophylactic regimen) showed better serum glucose levels and motor function, and lower morphological damage than animals that received SAC at the onset of reperfusion or animals in the DM+IR group.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

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Program #/Poster #: PSTR093.12/V15

Topic: D.03. Stroke

Support: CONACYT Grant A1-S-21433

Title: Neuroprotective effect induced by Psilocybe cubensis after cerebral ischemia in female rats.

Authors: *R. SÁNCHEZ-THOMAS[1], S. BAUTISTA PÉREZ[4], S. OLVERA MENDOZA[2], I. URIÓSTEGUI SOTELO[1], C. A. SILVA-ISLAS[5], A. AVENDAÑO-ESTRADA[3], D. BARRERA-OVIEDO[1], M. GONZÁLEZ TRUJANO[6], P. MALDONADO[7];
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Abstract: Ischemic stroke is a leading cause of death and disability, and promoting neuroplasticity mechanisms is necessary to induce neuroprotection and recovery. Psychedelics, such as psilocybin, have been shown to induce neuroplasticity. Therefore, it was evaluated whether this compound could exert neuroprotective effects following brain damage, particularly in females. Results showed that administration of *Psilocybe cubensis* extract to female rats (IR_{PC}) improved motor deficits after 1 h of ischemia and 48 h of reperfusion, compared to animals without treatment (IR). Additionally, microPET analysis revealed different glucose uptake between the IR and IR_{PC} groups, indicating a neuroprotective effect on ischemic severity. On the other hand, to determine if neuroplasticity mechanisms are associated with these effects, neurotrophin signaling such as brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), protein kinase B (AKT), synaptogenesis (SYP and PSD95), and neurogenesis (DCX) factors were evaluated in the striatum. At this point, it is concluded that *P. cubensis* extract, probably mainly psilocybin, supports post-ischemic recovery, improving motor performance, effects that could be associated with neuroplasticity.

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Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

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Program #/Poster #: PSTR093.13/V16

Topic: D.03. Stroke

Support: CBF-2025-I-4046

Title: Hydrogen Sulfide Donor NaHS Modulates Renal H_2S-Producing Enzymes and the Renin-Angiotensin System Following Global Cerebral Ischemia-Reperfusion in Rats

Authors: *A. BAEZ GONZALEZ[1], L. D. BOSQUES MONDRAGÓN[2], A. M. VELAZQUEZ SALAZAR, Sr.[3], F. RINCON ZARAZUA[4], A. SÁNCHEZ-LÓPEZ[6], D. CENTURIÓN[5]; [1]Cinvestav Sede Sur, Mexico City, Mexico; [2]Farmacobiologia, Cinvestav Sede Sur, San Jerónimo Cuatro Vientos, Mexico; [3]Cinvestav Sede Sur, Ciudad de Mexico, Mexico; [4]Cinvestav Sede Sur, Ciudad de mexico, Mexico; [5]Pharmacobiology, Cinvestav Sede Sur, Mexico City, Mexico; [6]Farmacobiología, Cinvestav-Coapa, Mexico, Mexico

Abstract: Stroke is increasingly recognized as a systemic disease that induces injury in distant organs, including the kidney. Acute kidney injury is an important but understudied consequence of cerebral ischemia-reperfusion (I/R). Hydrogen sulfide (H_2S), an endogenous gasotransmitter with antioxidant, anti-inflammatory, and vasoprotective properties, may protect against ischemic damage. This study evaluated the effects of sodium hydrosulfide (NaHS), an H_2S donor, on renal H_2S-producing enzymes and renin-angiotensin system components following cerebral I/R.Male Wistar rats (250-300 g) were assigned to four groups (n=6/group): Sham+PBS, Sham+NaHS, I/R+PBS, and I/R+NaHS. Cerebral ischemia was induced by transient unilateral carotid artery occlusion followed by reperfusion. NaHS (3.1 mg/kg, i.p.) or vehicle was administered for seven days. Hemodynamic parameters were evaluated in conscious animals. Renal injury was assessed by triphenyltetrazolium chloride staining. Renal H_2S levels and the expression of cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), 3-mercaptopyruvate sulfurtransferase (3-MST), angiotensin II (Ang II), and angiotensin type 1 receptor (AT1) were determined by Western blot.Body weight remained unchanged among groups. Cerebral I/R increased arterial pressure and heart rate, whereas NaHS partially attenuated these alterations. Renal injury was significantly greater in I/R animals than in sham controls. Renal H_2S levels increased in the I/R+PBS group and were normalized by NaHS treatment. Expression of CBS and CSE was reduced after cerebral I/R, indicating impaired endogenous H_2S production, while NaHS restored both enzymes. In contrast, 3-MST expression remained unchanged. Cerebral I/R also increased renal Ang II and AT1 receptor expression, suggesting activation of the renin-angiotensin system. NaHS reduced both markers, although levels remained above those of sham animals.These findings indicate that cerebral ischemia-reperfusion induces renal injury associated with dysregulation of endogenous H_2S signaling and activation of the renin-angiotensin system. NaHS partially reversed these alterations by restoring H_2S-producing enzymes and reducing Ang II/AT1 overexpression. These results support a renoprotective role for H_2S signaling following stroke and suggest that H_2S donors may represent a potential therapeutic strategy to limit kidney damage after cerebral ischemia.

Disclosures: A. Baez Gonzalez: None. **L.D. Bosques Mondragón:** None. **A.M. Velazquez Salazar:** None. **F. Rincon Zarazua:** None. **A. Sánchez-López:** None. **D. Centurión:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.14/V17

Topic: D.03. Stroke

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Title: Sustaining microglial reparative function enhances stroke recovery

Authors: *J. TSUYAMA[1], T. SHICHITA[2];
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Abstract: Neurological symptoms after brain injury can remain as lifelong detrimental sequelae since most spontaneous brain recovery disappears within a few months after brain injury. However, cellular and molecular mechanisms that diminish spontaneous brain functional recovery remain unknown. Microglia play an essential role in recovery processes after brain injury. Insulin-like growth factor 1 (IGF1) is a representative neurotrophic factor produced by post-stroke microglia that promotes synaptogenesis and remyelination. We discovered by cellular fate analysis that reparative microglia persisted in the post-stroke brain even after losing their reparative function. Through epigenetic analysis, ZFP384 was identified as a pivotal transcriptional regulator that diminished recovery phase-associated gene expression in reparative microglia, turning them into dysfunctional cells that lost reparative functions. Antisense oligonucleotides targeting Zfp384 sustained the broad range of neural repair effects of microglia and enhanced stroke recovery, even in the chronic phase of ischemic stroke recovery. Thus, therapeutics that prevent myeloid reparative immunity from losing its beneficial functions sustain brain functional recovery.

Disclosures: J. Tsuyama: None. **T. Shichita:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.15/V18

Topic: D.03. Stroke

Support: PhRMA Foundation, Predoctoral Fellowship
NEI R01EY035658
NEI R00 EY029373-03
CTSA 5T32TR004918-02

Title: Blockade of CD47/SIRPα Signaling Improves Efferocytosis and Reduces Brain Injury After Ischemic Stroke

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Abstract: Ischemic stroke remains one of the major causes of mortality and long-term disability worldwide. Although treatments such as tissue plasminogen activator (tPA) and mechanical thrombectomy have improved patient outcomes, many individuals still experience lasting neurological impairments. Post-stroke inflammation and inefficient removal of dead or dying cells through efferocytosis contribute to secondary brain injury. Microglia and macrophages, the primary immune cells of the central nervous system, are essential for clearing cellular debris and limiting inflammatory damage. However, the CD47/SIRPα signaling pathway can interfere with this process by delivering a "don't eat me" signal that prevents phagocytes from engulfing injured cells.In this study, we examined whether inhibiting the CD47/SIRPα pathway could improve recovery after ischemic stroke. Using transient middle cerebral artery occlusion (tMCAO) murine model, we observed a rapid upregulation in CD47 expression within the infarct core following injury. Treatment with neutralizing antibodies against either CD47 or SIRPα significantly reduced infarct volume. Notably, SIRPα blockade produced a greater reduction in tissue damage and was associated with sustained improvements in both cognitive and motor function. Fluorescence tracing demonstrated that SIRPα antibodies crossed the blood-brain barrier after stroke.Additionally, mice with myeloid cell-specific deletion of SIRPα developed smaller infarcts, further supporting the role of this pathway in regulating the clearance of damaged cells and post-stroke inflammation. Collectively, these findings indicate that targeting the CD47/SIRPα axis, particularly through SIRPα inhibition, enhances neuroprotection and promotes functional recovery after ischemic stroke. Given that anti-CD47 and anti-SIRPα antibodies have already demonstrated favorable safety profiles in cancer clinical trials, their alternative use for stroke treatment represents a promising therapeutic strategy.

Disclosures: C. Morris: None. **A. Fouda:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.16/Web Only

Topic: D.03. Stroke

Title: Neuraminidase Inhibition Preserves Sialylation and Attenuates Synaptic Loss Following Subarachnoid Hemorrhage

Authors: *A. S. REGNIER-GOLANOV[1], **N. KVIRKVELIA**[3], M. CLAXTON[4], D. ABE[2], E. V. GOLANOV[5], G. W. BRITZ[6];
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Abstract: Subarachnoid hemorrhage (SAH), i.e. blood accumulation within the subarachnoid space, has detrimental neurological consequences. Various mechanisms contribute to post-SAH pathology including synaptic loss in hippocampus. We hypothesized that activation of neuraminidases, which remove terminal sialic acids from the neuronal glycocalyx, promotes complement and glial activation, leading to synapse loss and neuraminidase inhibition would preserve sialylation and mitigate SAH-induced neuropathology. mRNA and protein expression of neuraminidase 1 and 3 (NEU1 and NEU 3) following SAH were investigated in mice by RNAscope and immunohistochemistry. NEU1 mRNA expression was significantly increased in SAH mice compared to Sham controls, with elevations of 32.5% (p=0.03, n=4) in the hippocampal molecular layer (ML), 101.64% (p=0.01, n=4) in the stratum lacunosum moleculare (SLM), and 50.86% (p=0.03, n=4) in the stratum oriens (SO). NEU3 mRNA expression showed comparable increases. NEU1 and NEU3 protein staining closely mirrored their mRNA distribution and displayed characteristic punctate staining. Desialylation due to activation of neuraminidases following SAH was assessed using lectins recognizing terminal glycans, such as maackia amurensis agglutinin (MAA), specific for α2,3-linked sialic acids and peanut agglutinin (PNA) specific for terminal β-galactose residues. Brain sections from SAH mice displayed 2.34-fold (p=0.04, n=3), increase of PNA binding and decreased MAA binding, consistent with the loss of terminal sialic acids and the exposure of underlying galactose residues. To prove role of neuraminidases in the development of SAH associated pathology, group of mice (n=3) received intraventricular injection of the pan-neuraminidase inhibitor 2,3-didehydro-2-deoxy-\(N\)-acetylneuraminic acid (DANA, 7.8 µg in 5µl of CSF) 24 hours prior to SAH induction. DANA preserved terminal sialic acids, evidenced by increased MAA binding across multiple hippocampal layers and reduced terminal galactose exposure. DANA-treated animals exhibited increases in MAA binding of 67.79% (p=0.002) in the ML and 56.59% (p=0.03) in the SLM layers. Importantly, DANA also prevented synaptic loss, resulting in a 2.25-fold increase (p=0.01, n=3) in PSD95-positive puncta in inhibitor injected mice compared with untreated SAH mice. These findings suggest that neuraminidase activation contributes to glycocalyx remodeling and synaptic loss following SAH. Pharmacological neuraminidase inhibition preserved sialylation and reduced synaptic pruning, suggesting a promising therapeutic strategy for mitigating the neurological consequences of SAH.

Disclosures: A.S. Regnier-Golanov: None. **N. Kvirkvelia:** None. **M. Claxton:** None. **D. Abe:** None. **E.V. Golanov:** None. **G.W. Britz:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.17/V19

Topic: D.03. Stroke

Support: NIH P20GM121176
NIH R01NS136494

Title: Zinc is Essential for Post-Recanalization Brain Recovery Following Ischemic Stroke

Authors: *R. PAN[1], Y. YANG[2], K. J. LIU[1];
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Abstract: Background and Purpose: Although recanalization therapies, such as thrombolysis and thrombectomy, have significantly improved acute ischemic stroke outcomes, many patients continue to experience poor recovery despite successful reperfusion, highlighting the lack of effective therapeutic strategies targeting the post-recanalization recovery phase. While zinc is essential for cellular repair and tissue function, its role in post-stroke recovery following recanalization remains unclear. Here, we investigated whether zinc supplementation during the recovery phase improves functional and histological recovery after ischemic stroke. **Methods:** Transient ischemic stroke was induced in rats by 90-minute middle cerebral artery occlusion (MCAO), followed by reperfusion. To selectively modulate zinc levels during the recovery phase, animals received either $ZnSO_4$ supplementation or the zinc chelator N,N,N′,N′-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) on days 7 and 10 post-stroke. At 14 days post-stroke, survival, neurological function, infarct volume, and neuronal and vascular densities were evaluated. **Results:** Zinc supplementation delivered significant benefits when administered during the recovery phase, significantly improving survival and neurological function at 14 days post-stroke. Conversely, zinc depletion produced profound deterioration, with markedly worse survival and neurological outcomes. Notably, zinc-treated animals showed robust increases in neuronal and vascular densities despite unchanged infarct volume. In contrast, zinc chelation exacerbated tissue injury, enlarged infarct size, and severely compromised neuronal survival, underscoring the essential role of zinc in post-stroke brain recovery. **Conclusions:** Our findings establish that zinc is essential for post-stroke recovery following recanalization. Importantly, the ability of zinc supplementation to improve outcomes when administered during the recovery phase highlights a clinically relevant opportunity to improve recovery after reperfusion. These results position zinc supplementation as a promising translational strategy to improve functional recovery after ischemic stroke.

Disclosures: R. Pan: None. **Y. Yang:** None. **K.J. Liu:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.18/V20

Topic: D.03. Stroke

Support: NIH 1R01NS138259
NIH R01NS142187
CIHR DFD-187707

Title: Single cell multiome and spatial transcriptomics reveal intranasal elovanoids preserve homeostatic phenotypes and limit damage after ischemic stroke

Authors: *J. JI, B. GILES, M.-A. KAUTZMANN, S. BHATTACHARJEE, A. JACOTTE-SIMANCAS, G. SKIPPER, R. BOUDREAUX, C. VIEIRA, L. S. BELAYEV, N. G. BAZAN; LSU Hlth. New Orleans, New Orleans, LA

Abstract: Ischemic stroke triggers spatially heterogeneous inflammatory, vascular, glial, and neuronal responses that determine whether penumbral tissue undergoes degeneration or recovery. Elovanoids (ELV) are lipid mediators with demonstrated neuroprotective effects, yet their cell-type-specific mechanisms remain incompletely defined. We integrated single-cell multiome profiling with high-resolution spatial transcriptomics to determine how intranasal ELV protects the post-ischemic rat brain after experimental stroke. Male Sprague-Dawley rats (3-4 months) underwent transient middle cerebral artery occlusion (MCAo; 2h) or sham surgery and received ELV-N34 (20 µg, intranasal) or vehicle at 1, 24, and 48h. Neurological assessment was performed daily for 3 days, and brains were collected for single-cell multiome and Xenium spatial transcriptomic analyses. Across both transcriptomic datasets, ELV attenuated neuronal loss and shifted the injured microenvironment toward homeostatic and reparative cell states. ELV reduced disease-associated microglia expressing *Spp1, Gpnmb, Lgals3, Clec7a, and Cd68*, while increasing homeostatic-like microglia and suppressing inflammatory signaling. ELV limited neutrophil infiltration and IgG leakage, preserved SMI-71-positive blood vessels, and stabilized the cortical neurovascular unit. In astrocytes, ELV reduced cortical cell loss and upregulated genes associated with synaptic organization. Oligodendrocyte-lineage analyses showed reduced immune-marker-expressing oligodendrocytes and OPCs, with preservation of differentiating and myelinating oligodendrocytes, suggesting support for post-ischemic repair. Neuronal analyses revealed partial preservation of glutamatergic and GABAergic neurons, reduced apoptosis, and increased pro-survival and synaptic gene expression. Together, ELV limits expansion of the ischemic core by suppressing damaging inflammatory and stress responses, preserving vascular integrity, and promoting coordinated homeostatic states across glial and neuronal populations. This integrated single-cell and spatial transcriptomic framework identifies ELV-mediated remodeling of the ischemic penumbra as a coordinated multicellular mechanism of neuroprotection after ischemia-reperfusion injury.

Disclosures: J. Ji: None. **B. Giles:** None. **M. Kautzmann:** None. **S. Bhattacharjee:** None. **A. Jacotte-Simancas:** None. **G. Skipper:** None. **R. Boudreaux:** None. **C. Vieira:** None. **L.S. Belayev:** None. **N.G. Bazan:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.19/V21

Topic: D.03. Stroke

Support: IBRO ISM Grant 00004

Title: Effects of a full-spectrum extract of Cannabis sativa 1:1 (CBD:THC) in patients with chronic sequelae of ischemic stroke.

Authors: *G. M. XAIA, Avila[1,2];
[1]Univ. Federal da Integração Latino-americana - UNILA, Foz do Iguaçu, Brazil; [2]ILACVN, Foz do Iguaçu, Brazil

Abstract: This project stems from the need to explore new therapeutic approaches for the treatment of chronic sequelae resulting from ischemic stroke, more specifically spasticity, chronic pain, cognitive and motor deficits, which represent a significant challenge for healthcare systems and the quality of life of affected patients. The objective of this project is to evaluate the effects of treatment with Cannabis sativa CBD:THC extract on spasticity, pain, cognitive/motor deficits, and decreased functionality in patients with chronic sequelae of stroke, as well as to observe the clinical, symptomatic, and biochemical safety profile of the treatment. This is an experimental, open-label, analytical, prospective case series study. The study is being conducted at UNILA, in the Cannabis and Psychedelics Laboratory (LCP), in Foz do Iguaçu, Paraná. Inclusion criteria included having had stroke confirmed by neuroimaging exams; at least 1 year passed since stroke; and never practiced physiotherapy or for at least 1 year before the study. The target age range is 50 to 70 years. Exclusion criteria include: presence of other associated neurological diseases; individuals with severe psychiatric illnesses; use of cannabis derivatives in the 3 months prior to the start of the study; pregnant women; and breastfeeding women. The experimental product consists of a full-spectrum extract of Cannabis sp. with an initial concentration of 1 mg/mL CBD and 1 mg/mL THC, which can reach up to 300 mg CBD and 30 mg THC according to the tolerability profile of each individual. This administration will occur over a period of 180 days. All clinical evaluations will be performed at eight time points: T0, T1, T30, T60, T90, T120, T150, and T180. Laboratory evaluations will be analyzed at T1 and T180. The results we have so far are that the project was approved by the Ethics Committee and began recruiting patients through a pre-screening. Those selected underwent final screening. Meetings with the sponsoring company secured biochemical tests, cannabis extracts, and publication fees. The Redcap platform was implemented for data collection, with layout and database approved by the statistician. We will have and show more results until the meeting. With stroke being the second leading cause of death worldwide and current treatments for its after-effects are still limited, cannabinoids emerge as a possible therapeutic alternative. It is hoped that the proposed experimental treatment will help reduce spasticity and pain, as well as provide cognitive and functional benefits, promoting a better quality of life for patients.

Disclosures: G.M. Xaia: None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.20/V22

Topic: D.03. Stroke

Support: Seed fund from Mount Sinai (#02482323)

Title: Targeting NETs Enhances Penumbra Reperfusion and Oxygenation After Ischemic Stroke in Aged Mice

Authors: *J. YIN[1], M. WU[2], J. WHITE[5], J. MOCCO[3], M. WATERS[4];
[1]Neurol., Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Icahn Sch. of Med. at Mount Sinai, Icahn School of Medicine at Mount Sinai, NY; [3]Neurosurg., Icahn Sch. of Med. at Mount Sinai, New York, NY; [4]Neurol., Icahn Sch. of Med. at Mount Sinai, Icahn School of Medicine at Mount Sinai, NY; [5]Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Background: Stroke is a leading cause of global mortality and disability. Large vessel acute ischemic strokes (AIS) contribute to 95% of mortalities and 62% of long-term disability in stroke patients. Despite the efficacy of endovascular thrombectomy (EVT) for large vessel acute AIS, many patients suffer from "futile recanalization," where distal micro-perfusion fails despite successful vessel opening. Futile recanalization remains a significant clinical challenge in AIS treatment. Neutrophil extracellular traps (NETs) are a primary driver of this microvascular obstruction. While DNase I has shown promise as a neuroprotective agent, evidence regarding its ability to improve penumbral reperfusion and oxygenation in aged stroke models is currently lacking. Method: Acute ischemic stroke (AIS) was induced in aged C57BL/6 mice. Following reperfusion, mice received immediate intra-arterial DNase I via the internal carotid artery. Real-time cerebral blood flow and penumbral oxygen concentration were monitored for 10 minutes post-treatment using a Unisense microprofiling oxygen microsensor. At 24 hours, we assessed neurological function, cerebral infarct volume, and NET markers. Results: DNase therapy significantly increased ischemic penumbra oxygen levels and cerebral blood flow immediately following treatment. At 24 hours post-stroke, DNase-treated mice exhibited improved neurological outcomes compared to age-matched vehicle controls, evidenced by lower neurological deficit scores and increased latency to fall in the wire hang test. Furthermore, DNase administration resulted in a significant reduction in cerebral infarct volume and a marked decrease in both neutrophil and NET density within the brain parenchyma and microvasculature. Conclusion: Our findings provide direct evidence that intra-arterial DNase therapy restores penumbral oxygenation and enhances cerebral reperfusion, resulting in improved neurological outcomes following large vessel occlusion in aged mice. These results support the potential clinical utility of catheter-delivered DNase as an adjunctive therapy to improve reperfusion efficacy in acute ischemic stroke.

Disclosures: J. Yin: None. **M. Wu:** None. **J. White:** None. **J. Mocco:** None. **M. Waters:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.21/V23

Topic: D.03. Stroke

Title: Engineering iNSC-Derived Extracellular Vesicles Fused with Platelet Membranes for Ischemic Stroke Therapy

Authors: *Y. NING;
Tongji Univ., shanghai, China

Abstract: <META NAME="author" CONTENT="圆梦 宁"> **Engineering iNSC-Derived Extracellular Vesicles Fused with Platelet Membranes for Ischemic Stroke Therapy**Yuanmeng Ning[1ǂ], Xiangyu Li[1ǂ], Xiaohuan Xia[1*], Jialin C. Zheng[1*] Translational Research Center, Shanghai Yangzhi Rehabilitation Hospital affiliated to Tongji University School of Medicine, Shanghai 201613, China.**Purpose:** Ischemic stroke is a leading cause of death and disability, yet current treatments fail to simultaneously restore cerebral blood flow (CBF) and promote long-term neurovascular repair. Pericytes, central regulators of cerebral microvessels, critically influence stroke pathophysiology. Inspired by platelets' natural targeting of injured vasculature, we developed a platelet membrane (PM)-decorated, Nimodipine (NIM)-loaded induced neural stem cell-derived extracellular vesicle (PM-EV-NIM) for ischemic stroke therapy.**Methods:** PM was obtained via freeze-thaw cycles; iNSC-EV was isolated by ultracentrifugation and characterized by bio-TEM, DLS, and WB. PM-EV-NIM was prepared by membrane extrusion. MCAO was induced by suture occlusion. Sensorimotor function was assessed by rotarod and balance beam tests; cognitive function by novel object recognition and Morris water maze. Targeting ability was evaluated by near-infrared imaging. Infarct volume was measured by TTC staining and MRI. CBF was monitored by laser speckle imaging. Brain tissue was analyzed by immunofluorescence, RT-qPCR, and WB. **Results:** PM-EV-NIM effectively targeted cerebral vascular injury regions through Itgb3 on PM binding to highly expressed Pdgfrb on pericytes. Treatment rapidly improved CBF, reduced infarct volume and neurological deficits, and enhanced motor and cognitive recovery in MCAO mice. This nanoplatform immediately inhibited pericyte contraction to restore CBF, while iNSC-EV cargo delivered functional proteins to ameliorate long-term pericyte injury. **Conclusion:** PM-EV-NIM offers significant translational potential by enhancing targeted drug delivery and providing multimodal treatment, offering promising new strategies for ischemic stroke management.

Disclosures: Y. Ning: None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.22/V24

Topic: D.03. Stroke

Support: 23IPA/AHA
23TPA/AHA
25TPA/AHA
26BIPA/AHA

Title: SGLT-2 inhibition preserves neurovascular integrity and mitigates ischemic brain damage in chronic kidney disease

Authors: *B. CHELLUBOINA[1], A. BODA[2], K.-K. MAK[3];
[1]Univ. of Illinois, Chicago, IL; [2]Univ. of illinois chicago, Chicago, IL; [3]Univ. of Illinois Chicago, Chicago, IL

Abstract: Stroke frequently coexists with chronic kidney disease (CKD). CKD, even in the absence of diabetes, primes endothelial dysfunction and pericyte loss, which compromises the neurovascular integrity and worsens brain damage and disability after stroke. Our recent studies showed the potential of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor dapagliflozin to regulate post-stroke neuroinflammation in CKD+Stroke. In the current study, we extended our investigation to determine the effect of preconditioning or delayed post-stroke SGLT-2 inhibition after CKD+Stroke on vascular integrity and brain damage. Adult C57BL/6J mice were subjected to 2 weeks of CKD followed by induction of stroke by transient middle cerebral artery occlusion (MCAO) for 35 minutes. The SGLT-2 inhibitor (Dapagliflozin) was administered either as a preconditioning agent (initiated at 2 weeks of CKD and 3 days before MCAO) or as delayed-phase therapy (initiated on post-stroke days 1-3). On post-stroke day 7, Brain damage was assessed using T2-weighted MRI, and tissues were collected for the assessment of neurovascular integrity. Circulatory profiling for kidney disease and inflammatory markers was performed to ensure CKD severity and stroke-mediated changes. CKD alone significantly increased vascular damage by reducing cerebral claudin-5 and occludin levels at 1 & 2 weeks of CKD, suggesting the direct impact of CKD on neurovascular integrity. We extended our study after stroke, untreated CKD+Stroke mice showed the lowest expression of claudin 5 and occludin, whereas both pre- and post-SGLT-2 inhibition restored these vascular integrity markers. These findings are consistent with stroke neuroprotection studies on the BBB integrity, which is crucial, particularly in the CKD+Stroke, a high-risk setting where renal disease and cerebral ischemia likely act together to amplify vascular injury. Additionally, the same datasets also showed suppression of key proinflammatory markers at the delayed phase of CKD+Stroke. Cerebral TLR-4 and TNF-α mRNA expression were markedly upregulated in CKD+Stroke, but both markers were reduced by SGLT-2 inhibition, with a greater reduction in pre-treatment than post-treatment; both remained protective relative to no treatment. These findings suggest a mechanistic link in which SGLT-2 inhibition mitigates neurovascular injury and curtails innate immune activation, thereby reducing secondary injury and functional deficits.

Disclosures: B. Chelluboina: None. **A. Boda:** None. **K. Mak:** None.

Poster

PSTR093: Stroke Recovery: Mechanisms and Pharmacological Approaches

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR093.23/V25

Topic: D.03. Stroke

Support: NIH: R01NS125074
NIH: R01AG083164

Title: Infiltrating monocyte derived macrophages does not survive long term in stroke brain despite their dominance in the acute ischemic core

Authors: *H. MA;
Univ. of Cincinnati, Cincinnati, OH

Abstract: Background Ischemic stroke elicits a strong neuroinflammatory response characterized by activation of microglia and infiltration of monocytes-derived macrophages (iMM), which have been speculated to have differential functions in stroke. However, because the gene expression profiles of microglia and iMM overlap in the injured brain, distinguishing these two cell populations has posed a challenge for the field. Methods Using a recently characterized microglia-specific *TMEM119*^{CreER}-Ai14 tdTomato reporter mouse model and single cell RNA sequencing (scRNA-seq) analysis, we prelabeled microglia in the CNS prior to stroke, enabling detailed characterization of the transcriptomic and spatial distributions of microglia vs iMM across different stages of post-stroke. ScRNA-seq findings were validated through immunohistochemistry, RNAscope, and animal models. Results Here, we report that microglia and iMM are enriched at distinct locations and exhibit differential temporal dynamics in the stroke brain. Despite previous hypothesized long-term survival of iMM and their proposed transition to a more-microglia like profile in chronic stroke brain, our genetic tracing data unambiguously reveals that iMM does not survive in the chronic stroke brain past 30 days. The sustained activated IBA1^{+} cells are nearly exclusively microglia in chronic stroke brain. Additionally, scRNA-seq further revealed distinct transcriptomic states between microglia and iMM at D7 and D14, which show overlapping and distinct cell-cell interactions with other immune cells in the stroke brain. Genetic tracing also allowed us to identify novel markers for activated microglia vs iMM in the acute stroke brain such as *Gm21188*, which could a potential useful marker for both identification and genetic targeting of highly activated microglia or iMM in stroke and other CNS diseases. Functionally, myeloid specific *Igf1* iKO mice show expedited sensorimotor function recovery but worsened anxiety-like behavior. Conclusions In summary, *Tmem119*^{CreER}-Ai14 tdTomato reporter mouse line is a useful tool for the field to clearly delineate the cellular dynamics and transcriptomic profiles of resident microglia vs iMM in a variety of CNS pathological conditions, which could have broad implications beyond stroke studies. Moreover, we have characterized novel subtypes and markers for activated microglia and iMM. This study provides valuable insights for future investigations aimed at modulating

microglia *vs* iMM, and their intercellular communication to promote stroke resolution and functional recovery in vivo.

Disclosures: H. Ma: None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.01/V26

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Effects of Non-Invasive Spinal Neuromodulation With Exercise on Gut Microbiome Diversity in Individuals with Spinal Cord Injury

Authors: *P. BARATH[1], E. BIELER[2], S. SAMEJIMA[3];
[1]Univ. of Washington, Seattle, WA; [2]Univ. of Washington, Lake Forest Park, WA; [3]Rehabil. Med., Univ. of Washington, Seattle, WA

Abstract: Spinal cord injury (SCI) is associated with autonomic dysfunction, including gastrointestinal dysregulation and alterations to the gut microbiome. The gut microbiome plays an important role in immune, metabolic, and gastrointestinal health, yet little is known about how neuromodulatory and exercise-based rehabilitation interventions influence microbial diversity following SCI. This study examined whether combined transcutaneous spinal cord stimulation (tSCS) and arm-cycle exercise is associated with changes in gut microbiome richness in individuals with chronic SCI. Participants with chronic cervical or upper-thoracic motor-complete SCI completed a combined tSCS and arm-cycle exercise intervention. Stool samples were collected longitudinally and analyzed using microbiome sequencing. Microbial richness was quantified using observed species richness and the Chao1 richness estimator, which captures both observed and rare taxa. Paired analyses were performed using available pre- and post-intervention samples. Observed species richness increased across all six participants following the intervention. Richness increased from 144 to 172, 109 to 211, 143 to 186, 112 to 119, 177 to 179, and 95 to 187 across participants. Mean observed species richness increased from 130.0 to 175.7 species, representing a 35.2% increase following intervention. Chao1 richness demonstrated more variable participant-specific responses, with increases observed in some participants and decreases or minimal changes in others. These preliminary findings suggest that combined tSCS and exercise may influence gut microbial richness in individuals with chronic SCI. The consistent increase in observed species richness across participants supports further investigation into interactions among neuromodulation, exercise, autonomic function, and the gut microbiome. Future studies incorporating larger cohorts, sham-controlled designs, dietary standardization, and longitudinal follow-up are needed to determine whether microbiome alterations represent adaptive remodeling or potential therapeutic targets for improving gastrointestinal and overall health after SCI.

Disclosures: P. Barath: None. **E. Bieler:** None. **S. Samejima:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.02/V27

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Effects of Transcutaneous Spinal Cord Stimulation on Walking Outcomes in Spinal Cord Injury: a Meta-Analysis and Systematic Review

Authors: *M. PATRIARCA[1], J. LIU[2];
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Abstract: Background: Transcutaneous spinal cord stimulation (tSCS) has emerged as a promising adjunct therapy for improving lower-limb motor and walking outcomes in people with spinal cord injury (SCI). However, findings across studies have been inconsistent, and a comprehensive meta-analysis remains lacking. Therefore, this systematic review with meta-analysis study aims to evaluate the effectiveness of tSCS on walking outcomes in SCI using randomized controlled and randomized crossover trial designs. **Methods:** A systematic review and meta-analysis was conducted examining randomized trials combining tSCS with rehabilitative interventions in individuals with SCI. PubMed, Embase, Web of Science, Scopus, PEDro, Cochrane Library, LIVIO, and WanFang were searched through April 2026. Two primary outcomes were walking speed assessed by the 10-meter walk test (10MWT) and walking endurance assessed by the 6-minute walk test (6MWT) and 2-minute walk test (2MWT). Lower extremity motor score (LEMS) was the secondary outcome. Random-effects meta-analyses were performed using Hedges'g effect sizes. Risk of bias and certainty of evidence were assessed using RoB 2 and GRADE analyses. Sensitivity analyses excluding crossover trials and studies utilizing the 2MWT were also performed. **Results:** Of 832 records identified, 6 studies comprising 232 participants met the inclusion criteria. Pooled analysis demonstrated significant improvements in walking speed ($g = 0.6215$, 95% CI [0.0189, 1.2241]), with a mean improvement of 0.0745 m/s in the 10MWT, which exceeded the published minimal clinically important difference for individuals with SCI (0.06 m/s). No significant gains in walking endurance ($g = 0.6292$, 95% CI [-0.1305, 1.3889]) or LEMS ($g = 0.4648$, 95% CI [-0.4978, 1.4274]) were observed. Sensitivity analysis excluding crossover trials demonstrated significant improvements in walking endurance ($g = 0.8341$, 95% CI [0.0006, 1.6676]). Risk of bias ranged from low to high, and certainty of evidence was low to very low. Substantial to high heterogeneity was observed across outcomes ($74.88 \leq I^2 \leq 86.83$). **Conclusions:** tSCS combined with rehabilitation produced significant and clinically meaningful improvements in walking speed compared with rehabilitation interventions alone for people with SCI. However, larger

high-quality clinical trials are needed to identify suitable populations, define biomarkers of response, and further clarify the role of tSCS in SCI rehabilitation.

Disclosures: M. Patriarca: None. **J. Liu:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.03/V28

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: RERC Grant 90REGE0025
The Reynolds Foundation

Title: Benchmarking Two Constant-Current Stimulators for Transcutaneous Spinal Cord Stimulation: An Intra- and Interday Comparison in an Able-Bodied Adult

Authors: *M. B. BAYRAM[1,2,3], A. BHEEMREDDY[2], G. F. FORREST[2,3];
[2]Tim and Caroline Reynolds Ctr. for Spinal Stimulation, [1]Kessler Fndn., West Orange, NJ;
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Abstract: Transcutaneous spinal cord stimulation (scTS) is a non-invasive modality that produces therapeutic effects comparable to invasive (epidural) stimulation, increasing spinal circuit excitability and aiding sensorimotor recovery after spinal cord injury (SCI). scTS effects can be refined through parameters such as current amplitude, pulse duration, frequency, and waveform configuration, and some stimulators add a 5-10 kHz carrier frequency to reduce discomfort. Because research groups worldwide use different devices to deliver stimulation, equivalent waveforms across devices are essential for replicable outcomes. This study benchmarked two of the most cited constant-current scTS stimulators in human research (verified in PubMed Central as of 12 June 2026), NeoStim-5 (Cosyma, Russia) and DS8R (Digitimer Ltd, Hertfordshire, UK), under identical high-carrier-frequency parameters. Recordings were obtained from one able-bodied male (42 yrs). EMG was recorded from seven right-leg muscles at 10 kHz, with the cathode (active) at T11/12 and the anode (return) at the ASIS. scTS pulses used a 5 kHz carrier, 1 ms pulse width, and 0.2 Hz rate, with intensity ramped from 0 to 100 mA in 5 mA steps (3 pulses per level). The two devices were tested on the same day, separated by a 15-minute interval, and the full protocol was repeated 4.5 months later, enabling intraday comparison between devices and interday comparison of each device across sessions. Both devices showed high linearity (cross-correlation > 0.99). For the upper-leg muscles, the relationship between stimulation amplitude and peak-to-peak EMG (p2pEMG) differed both intraday and interday: NeoStim-5 produced roughly 60% of the DS8R p2pEMG on the first day but roughly 120% on the second. This discrepancy may arise from factors such as

the cumulative effects of stimulation current on the spinal cord and day-to-day physiological variability. Further testing is needed to statistically characterize these differences.

Disclosures: M.B. Bayram: None. **A. Bheemreddy:** None. **G.F. Forrest:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.04/W1

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Buoniconti Fund to Cure Paralysis
Department of Health State of Florida

Title: Targeted Decoding of Lower-Limb Motor Intent and Spinal Afferent Recruitment After Spinal Cord Injury

Authors: *Z. BOOGAART[1], Y. LEI[2], R. FADLI[1], Y. ZHANG[3], M. MILOSEVIC[4];
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Abstract: Brain-computer interfaces (BCIs) and transcutaneous spinal cord stimulation (TSCS) are promising strategies for restoring lower-limb function after spinal cord injury (SCI). Effective closed-loop neuromodulation requires both accurate detection of intended movement and selective engagement of the corresponding spinal sensorimotor pathways. Here, we evaluate two complementary components of a targeted BCI-TSCS framework: limb-specific personalized decoding of lower-limb motor imagery from electroencephalography (EEG) and laterality-targeted recruitment of posterior root-muscle (PRM) reflexes using spatially configured TSCS. For cortical intent decoding, individuals with chronic incomplete SCI performed cued left- and right-ankle dorsiflexion motor imagery while EEG was recorded. A Dense Convolutional Transformer (EEG-Deformer) combined with subject-specific feature space fine-tuning was used to classify motor imagery tasks, including move versus rest, left versus right, and three-class left versus right versus rest decoding. Decoding performance was significantly above chance across tasks, with group-mean accuracy at 79.9±11.4%, supporting physiologically plausible limb-specific decoding interpretability. For spinal targeting, PRM reflexes were assessed during TSCS delivered with electrode configurations placed to preferentially recruit left-sided, midline, or right-sided spinal Ia afferent pathways. Laterality indices of PRM reflexes indicated that lateralized electrode placements preferentially biased recruitment toward the intended limb, whereas midline stimulation produced a more non-specific, and bilateral, recruitment pattern in both stronger and weaker limbs. Together, these findings suggest that cortical motor intent, and spinal afferent recruitment, can be lateralized after SCI. This work supports the development of a

targeted BCI-TSCS system that pairs decoding of limb-specific motor intent with spatially targeted afferent stimulation to reinforce residual corticospinal pathways and improve lower-limb neurorehabilitation.

Disclosures: Z. Boogaart: None. **Y. Lei:** None. **R. Fadli:** None. **Y. Zhang:** None. **M. Milosevic:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.05/W2

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Department of Defense
Bryon Riesch Paralysis Foundation
Buoniconti Fund to Cure Paralysis

Title: Brain-Controlled Transcutaneous Spinal Stimulation Restores Stepping Function By Potentiating Corticospinal Connectivity After Incomplete Spinal Cord Injury

Authors: *J. WHITEHAIR[1], R. FADLI[1], A. SASAKI[2], Z. BOOGAART[1], A. YUASA[1], H. SAITO[3], J. D. GUEST[4], M. MILOSEVIC[5];
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Abstract: Transcutaneous spinal cord stimulation (TSCS) facilitates locomotor function by activating dorsal root fibers and amplifying residual descending input. Integrating TSCS with a brain-computer interface (BCI) may further enhance neuromodulation by synchronizing cortical commands with spinal activation. We evaluated the feasibility and efficacy of BCI-triggered TSCS (BCI-TSCS) to improve lower-limb motor function and corticospinal connectivity in individuals with chronic (>6 months) incomplete spinal cord injury (iSCI) (T10 or above, AIS C or D) in two experiments: (1) single-session effects on corticospinal connectivity and stepping function, and (2) four-month therapeutic effects on walking performance. The BCI system used a single electroencephalography electrode to detect lower-limb motor imagery in real time and triggered TSCS when motor imagery was detected within 15 s; otherwise, the next trial proceeded without stimulation (success rate 83.3±4.6%). TSCS was delivered using a cathode over T11-L4 and an anode over the umbilicus or iliac crests at 25-150 mA to recruit dorsal sensory fibers. A randomized crossover trial compared a single 30-min BCI-TSCS session with a matched TSCS-only condition in 10 participants. Outcomes included motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) to assess corticospinal connectivity and the lower extremity motor coordination test. BCI-TSCS significantly increased corticospinal

excitability and motor performance beyond TSCS-only, supporting the role of temporally coordinated cortical and spinal activation in inducing associative Hebbian plasticity. A feasibility clinical study evaluated BCI-TSCS for improving walking after iSCI. Four participants (AIS D T10 and above) completed 1 month of conventional walking therapy followed by 3 months of BCI-TSCS (12 sessions/month). Functional outcomes (10-meter walk test; 6-minute walk test) showed clinically meaningful improvements. Walking speed increased by 0.13 m/s and endurance improved by 51.75 meters, both exceeding the minimal clinically important difference. Kinematic and muscle synergy analyses indicated improved gait quality. These functional gains were associated with increased TMS-MEPs, suggesting enhanced corticospinal connectivity. Our findings support BCI-TSCS as a promising neuromodulation strategy to enhance motor function and corticospinal connectivity, supporting the translation potential of BCI-TSCS neuromodulation in chronic iSCI.

Disclosures: J. Whitehair: None. **R. Fadli:** None. **A. Sasaki:** None. **Z. Boogaart:** None. **A. Yuasa:** None. **H. Saito:** None. **J.D. Guest:** F. Consulting Fees (e.g., advisory boards); ONWARD Medical. **M. Milosevic:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.06/W3

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Department of Defense

Title: Immediate improvements in gait assistance and walking symmetry through non-invasive brain-controlled spinal stimulation in incomplete spinal cord injury

Authors: *N. KAMARA[1], R. FADLI[1], Z. BOOGAART[1], A. SASAKI[2], M. MILOSEVIC[3]; [1]Univ. of Miami, Miami, FL; [2]The Univ. of Tokyo, Meguro-ku, Japan; [3]Univ. of Miami - Miami Project to Cure Paralysis, Miami, FL

Abstract: Spinal cord injury (SCI) disrupts the descending tracts responsible for voluntary movement, yet incomplete injuries often spare residual corticospinal connections that can be re-engaged to promote motor recovery. Transcutaneous spinal cord stimulation (TSCS) drives neuromodulation by activating these residual neural networks in the spinal cord to promote motor function. Integrating TSCS with a brain-computer interface (BCI) where motor command is paired with spinal stimulation may further reinforce these residual corticospinal pathways by delivering stimulation time-locked to the participant's movement intention, strengthening the functional link between cortical and spinal neurons. In this study, we evaluated the feasibility and assistive benefit of a closed-loop BCI-TSCS intervention during walking in four individuals with chronic incomplete SCI. We developed a BCI system that detects motor imagery from a

single electroencephalography (EEG) electrode. The BCI triggered TSCS for 3-5 s when motor imagery was detected within 15 s of a visual cue to step, achieving an overall detection success rate of 87.0±1.1%. TSCS was delivered through surface electrodes, with the cathode placed between the T12-L1, L1-L2, or L2-L3 vertebrae and the anode above the umbilicus. Stimulation intensity was set to 70-90% of motor threshold to assist stepping without causing involuntary movement. Each participant completed a single session in which walking performance was assessed during a 10-meter walk test (10MWT) and compared with a no-stimulation condition, with lower-limb kinematics captured by a motion-capture system. BCI-TSCS immediately improved walking performance, increasing stride length (581.7±141.3 mm) compared with no-stim (513.8±175.5 mm). Accompanying this improvement in overall stepping distance, gait symmetry also improved, as step length asymmetry (SLA) was significantly reduced with BCI-TSCS (0.041±0.009) compared with no-stim (0.090±0.019), reflecting more coordinated stepping between the stronger and weaker limbs rather than the stronger leg dominance observed without stimulation. These findings demonstrate the feasibility and efficacy of intention-driven BCI-TSCS for providing immediate improvements of lower-limb motor function in chronic incomplete SCI, supporting the use of closed-loop spinal neuromodulation that re-engages residual descending connections to enhance walking performance.

Disclosures: N. Kamara: None. **R. Fadli:** None. **Z. Boogaart:** None. **A. Sasaki:** None. **M. Milosevic:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.07/W4

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Tim & Caroline Reynolds Foundation

Title: Immediate and long-term effects of transcutaneous spinal cord stimulation on postural control during overground walking

Authors: *M. ANJARIA, A. BHEEMREDDY, M. RAVI, M. B. BAYRAM, G. F. FORREST; Tim & Caroline Reynolds Ctr. for Spinal Stimulation, Kessler Fndn., West Orange, NJ

Abstract: Activity based recovery training with transcutaneous spinal cord stimulation scTS has been shown to increase trunk postural control, enabling increased independent standing in individuals with spinal cord injury (SCI). Building on these findings, the objective of the present study was to evaluate changes quantifiable in postural control during walking with scTS over the course of overground gait training. Total body three-dimensional kinematics were evaluated for chronic incomplete SCI participants who completed gait training with and without scTS along with multi-channel EMG analysis. Multiple, targeted cohorts of scTS were delivered with

cathodes at the lumbosacral and thoracic spinal sites and bilateral anterior superior iliac spine as anodes. The stimulation waveforms consisted of a rectangular pulse (width of 1ms) with 5kHz carrier frequency. Individuals were tested before, at after training. Full-body kinematics (Motion Analysis, California) were collected while participants walked overground with and without scTS and surface EMG electrodes (Motion Lab Systems Inc., Baton Rouge, LA) for muscle activation were collected for lower extremity muscle groups. At baseline, prior to any training intervention, immediate effects of stimulation were observed, including correction of offsets in trunk center of mass (COM) excursions while walking overground. With continued gait training combined with scTS, further improvements in trunk COM control were evident, indicating enhanced postural stability during gait. These findings suggest that training with scTS when paired with targeted training, can dramatically facilitate both immediate and progressive improvements in trunk control and dynamic postural stability in individuals with SCI.

Disclosures: M. Anjaria: None. **A. Bheemreddy:** None. **M. Ravi:** None. **M.B. Bayram:** None. **G.F. Forrest:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.08/W5

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Wings for Life
Mission Yogurt

Title: Biomechanical Adaptations in Gait with Long-Term Transcutaneous Spinal Cord Stimulation and Locomotor Training

Authors: E. BIELER, S. SHRIVASTAV, R. P. HENDERSON, R. NAKAHARA, S. NASSON, C. T. MORITZ, *S. SAMEJIMA;
Univ. of Washington, Seattle, WA

Abstract: For individuals with motor-incomplete spinal cord injury (SCI), recovery of walking is a top rehabilitation priority; however, traditional approaches such as locomotor training (LT) often fail to meet patient goals. Transcutaneous spinal cord stimulation (tSCS) is a promising neuromodulation therapy now entering clinical use. Most studies assess the effects of tSCS using coarse measures like gait speed, but finer-scale analysis is needed to optimize individualized treatment. This study evaluated the impact of long-term lumbar and cervical tSCS combined with LT on lower-limb joint kinematics. Three participants were included: P1 (female, 59 years old, C5-6 AIS D, 15 years post-injury), P2 (male, 49 years old, C6 AIS C, 18 years post-injury), and P3 (male, 50 years old, C5 AIS D, 27 years post-injury). Primary mobility devices were powered wheelchair (P1), manual wheelchair (P2), and scooter (P3). P2 used a walker during testing. All

participants completed bodyweight-supported treadmill LT with tSCS delivered via the SpineX SCONE. Data were collected at baseline and post-intervention. For P1 and P2, baseline followed LT alone (18 and 12 sessions, respectively), and post-intervention followed 18 sessions of combined LT + lumbar tSCS and 18 sessions of combined LT + simultaneous lumbar and cervical tSCS. For P3, baseline was pre-therapy and post-intervention followed 9 sessions of LT alone and 14 sessions of LT + lumbar tSCS. Kinematics were captured using the OpenCap markerless motion capture system during self-paced walking. Walking performance was also assessed via the six-minute walk test (6MWT). Compared to baseline, P1 exhibited increased knee (7.9%) and ankle (1.9%) excursions and decreased hip excursion (−5.1%) post-intervention. P2 exhibited increased excursions at all joints, with the greatest change at the knee (knee 61.2%; hip 20.5%; ankle 4.3%). P3 exhibited increased hip excursion (16.1%) and decreased knee (−2.7%) and ankle (−8.6%) excursions. Only P3 demonstrated notable cadence change (109.7 to 123.2 steps/min) during self-paced walking. However, all participants improved 6MWT distance (P1: 415.1 to 558.2m; P2: 18.7 to 25.1m; P3: 340.7 to 380.4m). These findings suggest that different individuals have unique joint-level responses to tSCS and indicate that different movement strategies may underlie functional gains. This preliminary work supports the use of joint kinematics to guide more precise, data-driven tSCS parameter optimization.

Disclosures: E. Bieler: None. **S. Shrivastav:** None. **R.P. Henderson:** None. **R. Nakahara:** None. **S. Nasson:** None. **C.T. Moritz:** None. **S. Samejima:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.09/W6

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Neuromodulation for Motor function

Authors: *G. F. FORREST, C. A. ANGELI;
Kessler Fndn., West Orange, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) is a promising, non-invasive method of improving blood pressure (BP) instability among people with spinal cord injury (SCI). In this study, scTS was applied to cervical, thoracic, and lumbar spinal sites. Concurrently with stimulation, electromyogram (EMG) was recorded from trunk, upper, and lower extremity muscles. Continuous BP was also recorded and synchronized with muscle EMG and stimulation. *This case study presents the effect of i) targeted scTS on the BP and motor response for one individual with motor-incomplete SCI during one mapping session of scTS; ii) targeted scTS to address motor function and orthostatic hypotension during stand training.*

Disclosures: G.F. Forrest: None. **C.A. Angeli:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.10/W7

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH 1R03HD120505
NJ Commission on Spinal Cord Research CSCR25ERG009

Title: Frequency-Dependent Modulation of Lower-Limb EMG During Cardiovascular-Targeted Spinal Cord Transcutaneous Stimulation in Spinal Cord Injury

Authors: *E. ENGEL-HABER[1], A. BHEEMREDDY[2], M. B. BAYRAM[3], M. RAVI[2], G. F. FORREST[4];
[2]Ctr. for Spinal Stimulation, [3]Tim and Caroline Reynolds Ctr. for Spinal Stimulation, [4]CSS, [1]Kessler Fndn., West Orange, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) is increasingly used to raise blood pressure and improve cardiovascular regulation after spinal cord injury (SCI), yet the mechanisms underlying this effect remain under investigation. A leading hypothesis is that stimulation engages afferent fibers entering the spinal cord, which in turn recruit interneuronal circuits and sympathetic preganglionic neurons that contribute to the pressor response. However, thoracolumbar scTS may also activate spinal motor networks and lower-limb musculature, raising the possibility that stimulation-related changes in venous return contribute to the blood pressure response. Defining these secondary motor effects is important for interpreting cardiovascular-targeted stimulation paradigms and for optimizing multimodal neuromodulation strategies. We therefore examined lower-limb electromyographic (EMG) activity during scTS delivered for blood pressure modulation in individuals with chronic SCI. Participants underwent standardized seated mapping sessions in which stimulation was applied primarily over L1/L2 at 30, 40, or 50 Hz. Stimulation amplitude was increased up to 120 mA using monophasic 1 ms rectangular pulses with a 1 kHz carrier frequency. Surface EMG was recorded bilaterally from major leg muscles, and analyses focused on burst count, burst amplitude, and temporal activation patterns under conditions in which stimulation amplitude and systolic blood pressure were matched across comparisons. These data are being used to determine how stimulation frequency shapes motor excitability during cardiovascular-focused scTS and to clarify the extent to which autonomic and motor spinal networks may be co-engaged in chronic SCI.

Disclosures: E. Engel-Haber: None. **A. Bheemreddy:** None. **M.B. Bayram:** None. **M. Ravi:** None. **G.F. Forrest:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.11/W8

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIDILRR Grant (RERC #90RE5021-01-00)
NIDILRR Grant (ARRT #90ARHF0002)
the Tim Reynolds Foundation

Title: Associations between Spinal Evoked Potentials and Upper Extremity Function in Individuals with Cervical Spinal Cord Injury

Authors: *F. ZHANG[1,2], M. AGOSTINI[1], M. ANJARIA[1], A. BHEEMREDDY[1], M. RAVI[1], G. F. FORREST[1,2];
[1]Tim and Caroline Reynolds Ctr. for Spinal Stimulation,, Kessler Fndn., West Orange, NJ;
[2]Dept. of Physical Med. & Rehabil., Rutgers, New Jersey Med. Sch., Newark, NJ

Abstract: Spinal cord transcutaneous stimulation (scTS) has emerged as a promising neuromodulatory intervention for promoting recovery of upper extremity function following cervical spinal cord injury (SCI). Identifying objective neurophysiological markers that reflect residual sensorimotor function is critical for both characterizing injury-related impairments and informing the development of individualized stimulation strategies. This study investigated the association between upper extremity spinal evoked potentials (SEPs) elicited by targeted scTS and clinical measures of upper limb function in individuals with chronic cervical SCI prior to therapeutic intervention. Associations were evaluated between SEPs characteristics and standardized assessments including the International Standards for Neurological Classification of SCI Upper Extremity Motor Score (UEMS) and the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP). Moderate-to-strong correlations were observed between baseline UEMS and GRASSP scores and SEP peak-to-peak amplitudes at specific stimulation sites and muscles, suggesting that spinally evoked responses may capture aspects of preserved neural circuitry underlying upper extremity function. Establishing these relationships may facilitate the identification of neurophysiological biomarkers that can be used to optimize scTS parameters, personalize stimulation targeting, and improve the effectiveness of rehabilitation interventions. Further studies with larger cohorts and longitudinal follow-up are needed to determine the reliability, specificity, and predictive value of SEP measures for guiding and monitoring functional recovery after cervical SCI.

Disclosures: F. Zhang: A. Employment/Salary (full or part-time):; Kessler Foundation. **M. Agostini:** A. Employment/Salary (full or part-time):; Kessler Foundation. **M. Anjaria:** A. Employment/Salary (full or part-time):; Kessler Foundation. **A. Bheemreddy:** A. Employment/Salary (full or part-time):; Kessler Foundation. **M. Ravi:** A. Employment/Salary (full or part-time):; Kessler Foundation. **G.F. Forrest:** A. Employment/Salary (full or part-time):; Kessler Foundation.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.12/W9

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: MN Office of Higher Education - Spinal Cord Injury and Traumatic Brain Injury Research Grant Program (#165646)

Title: Cervical Epidural Stimulation Produces Reproducible Motor, Sensory, and Autonomic Recruitment Patterns in Chronic Cervical Spinal Cord Injury

Authors: *S. CHEONG[1], C. BROADBENT[2,1], Y. SHAM[3], U. SAMADANI[4];
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Abstract: Introduction: Epidural spinal cord stimulation (eSCS) has emerged as a promising neuromodulatory strategy for restoring function after spinal cord injury (SCI). While most clinical experience has focused on thoracolumbar stimulation targeting locomotion, the safety and therapeutic potential of cervical spinal cord stimulation (cSCS) remain poorly characterized. Concerns regarding proximity to critical respiratory and autonomic pathways have limited widespread adoption. We evaluated the safety, feasibility, and preliminary functional outcomes of cSCS in patients with chronic cervical SCI.Methods: We retrospectively reviewed five patients with chronic cervical SCI who underwent cervical epidural spinal cord stimulator implantation. Etiologies included motor vehicle collision, fall, gunshot injury, and cervical myelopathy. Postoperative programming utilized individualized tonic and burst stimulation paradigms optimized during multidisciplinary rehabilitation. Clinical outcomes included perioperative safety, motor and sensory responses, autonomic function, and rehabilitation performance.Results: Cervical stimulation was successfully implanted in all patients without major neurological complications. Stimulation produced reproducible motor and sensory recruitment involving the upper extremities, trunk, and, in some cases, lower extremities. Functional improvements included increased upper-extremity strength, enhanced hand activation, improved trunk stability, greater seated balance, and improved coordination during rehabilitation. One patient improved from ASIA A to ASIA D following implantation and rehabilitation. Improvements in autonomic regulation, including reduced dysautonomic episodes and improved blood pressure stability, were observed in selected patients. Device-related complications were limited to programming optimization challenges and one stimulator revision without neurological sequelae. No patient experienced stimulation-related neurological deterioration.Conclusions: Cervical epidural spinal cord stimulation appears safe and feasible in carefully selected patients with chronic cervical SCI. Stimulation generated reproducible motor, sensory, and autonomic responses with preliminary evidence of functional improvement. These

findings support further investigation of cervical neuromodulation as a strategy to enhance recovery and functional outcomes after cervical SCI.

Disclosures: S. Cheong: None. **C. Broadbent:** None. **Y. Sham:** None. **U. Samadani:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.13/W10

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: The Reynolds Foundation

Title: Frequency Characteristics of Intermuscular Coherence During Voluntary Independent Standing with Spinal Cord Epidural Stimulation

Authors: *A. BHEEMREDDY[1], M. ANJARIA[2], M. B. BAYRAM[2], M. RAVI[2], C. A. ANGELI[2], G. F. FORREST[2];
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Abstract: Spinal Cord Injury (SCI) can often lead to a loss of function and control for individuals below the level of injury. Lumbosacral spinal cord epidural stimulation (scES) combined with activity-based stand training (ABT) has been shown to improve the recovery of motor function and independent standing for people with complete or incomplete SCI. Intermuscular coherence (IMC) is a frequency-domain approach for determining the shared neural input of pairs of muscles by quantifying the synchronized motor unit activity. IMC can be further characterized into specific physiological frequency ranges for the alpha, beta, and gamma bands, which provides further insight into coupling of spinal motor pathways. An individual (27-year-old female) with chronic cervical incomplete SCI participated in an activity-based stand training with spinal cord epidural stimulation to improve standing. The participant was unable to stand unassisted with bilateral hip and knee joints at baseline, before the intervention. The study focused on individuals with SCI who perform scES+ABT to improve independent standing. The objectives of this study were to distinguish the frequency characteristics of IMC among lower-limb and pelvic muscle pairs during voluntary independent standing with scES, compared with standing without scES. Increases in alpha-, beta-, and gamma-band IMC were determined for knee- and ankle-related muscle pairs during volitional standing with scES, relative to volitional stranding without scES.

Disclosures: A. Bheemreddy: None. **M. Anjaria:** None. **M.B. Bayram:** None. **M. Ravi:** None. **C.A. Angeli:** None. **G.F. Forrest:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.14/W11

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: New York State Spinal Cord Injury Research Board C37719GG

Title: Recovery of pelvic postural control during standing by robotic postural stand training and spinal cord epidural stimulation in an individual with motor complete spinal cord injury

Authors: *E. REJC[1], I. OMOFUMA[1], C. A. ANGELI[1], A. BHEEMREDDY[1], S. ZDUNOWSKI[1], M. ANJARIA[1], S. HARKEMA[1], S. AGRAWAL[2], G. F. FORREST[1]; [1]Kessler Fndn., West Orange, NJ; [2]Columbia Univ., New York, NY

Abstract: Objective. Spinal cord epidural stimulation (scES) and activity-based recovery training can promote the recovery of standing motor function after motor complete spinal cord injury (SCI). In this population, and more generally after severe SCI, individuals regularly self-assist standing postural control by placing their hands on assistive devices such as walker or standing frame. In this study, we assessed the effect of robotic postural stand training with scES on the recovery of pelvic control during standing with free hands. **Methods.** An individual with chronic, clinically motor complete SCI (lesion level: Cervical 6) underwent assessment and training of standing postural control with scES and free hands within the robotic upright stand trainer (RobUST), which provided assistance-as-needed at the trunk and pelvis and real-time visual feedback. Trunk and pelvis displacement, ground reaction forces, and bilateral EMG activity of lower limb muscles were collected and analyzed. Robotic postural stand training with scES consisted of 40 sessions (1 hour/session) during which stable standing and self-initiated dynamic tasks were performed with the lower level of robotic assistance required to perform the task. **Results:** Prior to training, the participant was unable to achieve independent pelvic control while the trunk was constantly assisted by RobUST. However, independent pelvic control emerged after 30 training sessions with constant trunk assistance, and it was subsequently achieved also with trunk assistance-as-needed (i.e., assistive force provided only when the trunk moved beyond a preset virtual boundary). These improvements in pelvic control during standing were associated with lower limb muscle-specific changes in activation pattern. **Conclusion:** Robotic postural stand training with scES and free hands can facilitate the recovery of independent pelvic control during standing, which has critical implications for the recovery of functional mobility.

Disclosures: E. Rejc: None. **I. Omofuma:** None. **C.A. Angeli:** None. **A. Bheemreddy:** None. **S. Zdunowski:** None. **M. Anjaria:** None. **S. Harkema:** None. **S. Agrawal:** None. **G.F. Forrest:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.15/W12

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: National Natural Science Fund for Young Scholar (No. 82301657)
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Title: Redistribution of Neural and Muscular ^{18}F-FDG Uptake after the Epidural Electrical Stimulation Treatment in Spinal Cord Injury Individuals

Authors: *Q. YAO, B. ZHANG;
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Abstract: Background: Epidural electrical stimulation (EES) can restore lower-limb motor function after spinal cord injury (SCI), but its effects on distributed metabolic plasticity across the nervous system remain unclear. We used resting-state ^{18}F-FDG PET/CT to investigate metabolic reorganization after six months of EES-assisted rehabilitation in individuals with chronic SCI.**Methods:** Two individuals with chronic thoracic SCI received a 32-electrode epidural paddle array targeting the lumbar enlargement and underwent EES-assisted standing and overground walking training. Resting-state ^{18}F-FDG PET/CT was performed before implantation and after six months of rehabilitation with stimulation turned off. Metabolic changes were evaluated in the brain, spinal cord, and lower-limb muscles.**Results:** Both participants demonstrated improved lower-limb motor activation and rhythmic gait during EES. Resting-state cerebral metabolism showed individualized redistribution after rehabilitation. P1 and P2 exhibited increased metabolism in occipital regions and decreased metabolism across frontal, temporal, limbic, insula-opercular, and subcortical regions. In the spinal cord, ^{18}F-FDG uptake increased in EES-targeted segments while decreasing across most nonstimulated regions, indicating a redistribution of intraspinal metabolism toward stimulated networks. Electrode-row analysis further demonstrated enhanced metabolism in nearly all stimulated regions. In lower-limb muscles, cross-sectional muscle volume increased after rehabilitation, resulting in elevated total glycolytic activity despite modest reductions in resting SUVr. Total glycolysis increased by 19.8% in the psoas major, 30.7% in the iliacus, and 9.8% in thigh muscles.**Conclusions:** EES-assisted rehabilitation was associated with coordinated metabolic reorganization across cerebral, spinal, and muscular systems in individuals with chronic SCI. These findings suggest that motor recovery following neuromodulation may involve distributed brain-spinal-muscular metabolic

plasticity. Resting-state ^{18}F-FDG PET/CT may provide a useful biomarker for evaluating system-level adaptations induced by EES rehabilitation.

Disclosures: Q. Yao: None. **B. Zhang:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.16/W13

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: A staged feasibility framework for epidural spinal cord stimulation to modulate male sexual function after spinal cord injury

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Abstract: Sexual dysfunction is a common and quality-of-life-limiting consequence of spinal cord injury (SCI), yet current interventions rarely restore coordinated sexual function. Male erection, emission, and ejaculation depend on distributed spinal autonomic and somatic circuitry, suggesting that single-site stimulation may be insufficient for meaningful functional recovery. We performed a structured translational evidence map to link spinal stimulation targets with measurable endpoints and safety constraints for first-in-human feasibility testing. Peer-reviewed evidence on spinal sexual reflexes, SCI-associated sexual dysfunction, autonomic regulation, autonomic dysreflexia, and clinical spinal cord stimulation was organized into a target-endpoint-safety matrix across five domains: segmental target, putative pathway, expected functional response, measurable endpoint, and feasibility or safety constraint. The matrix identified three priority testing domains: sacral pathways associated with reflexogenic erection, thoracolumbar sympathetic pathways associated with emission and ejaculation, and autonomic/somatic monitoring required for safe stimulation escalation. Candidate endpoints included penile tumescence and rigidity, emission or ejaculation when applicable, stimulation threshold and tolerability, patient-reported sexual function and satisfaction, and cardiovascular monitoring for autonomic dysreflexia risk. The resulting framework supports a staged feasibility protocol using existing spinal cord stimulation hardware and clinical neuromodulation workflows to test sacral and thoracolumbar stimulation paradigms before development of a purpose-built dual-site device. By separating biological validation from custom hardware development, this evidence map provides a practical research pathway for evaluating dual-site spinal stimulation as a neuromodulatory strategy for male sexual function after SCI.

Disclosures: L.G. Jiracek: A. Employment/Salary (full or part-time):; University of Florida, IntimaStim. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IntimaStim.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.17/W14

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Buoniconti Fund
Morton Cure Paralysis Fund

Title: Immediate Upper-Limb Assistance and Rapid Corticospinal Facilitation Through BCI-Driven Epidural Spinal Stimulation After Chronic Tetraplegia

Authors: *R. FADLI[1], Z. BOOGAART[1], A. SASAKI[3], A. YUASA[1], H. SAITO[4], M. F. BANDRES[2], R. DE FREITAS[5], N. MACELLARI[6], E. PIRONDINI[7], J. D. GUEST[9], M. CAPOGROSSO[8], M. MILOSEVIC[10];
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Abstract: Voluntary movement relies on closed-loop motor control within the central nervous system, a connection that is disrupted at the spinal level following spinal cord injury (SCI). Epidural spinal cord stimulation (ESCS) can modulate spinal sensorimotor circuits to facilitate residual motor output following spinal cord injury (SCI), yet most approaches deliver stimulation continuously rather than using the user's own neural activity. Integrating ESCS with a brain-computer interface (BCI) that decodes volitional motor intent in real time may improve neuroprosthetic efficacy and neuroplastic potential by aligning stimulation onset with attempted movement. Here, we present assistive and single-session neurophysiological effects of an implantable BCI paired with cervical ESCS in three (n=3) individuals with chronic cervical SCI (C3-C5 neurological levels; AIS A-D). Percutaneous epidural stimulation leads were implanted in the right epidural space caudal to the injury targeting upper-limb sensorimotor circuits through dorsal rootlets spanning C5-T1, and a BCI decoded motor imagery from electrocorticography (ECoG) signals to trigger ESCS in real time during activity-based therapy, with a decoding success rate of 83.8±4.2%. Assistive effects were assessed by comparing grip force, EMG activity, and 3D reaching kinematics across no-stimulation, tonic ESCS, and BCI-ESCS conditions. Single-session neurophysiological effects were assessed before and immediately after each session using motor evoked potentials (MEPs) and posterior root muscle (PRM) reflexes to evaluate corticospinal and spinal circuit excitability, using an interleaved crossover design with two sessions per condition. BCI-ESCS provided immediate assistive effects, improving grip force as well as reaching smoothness and accuracy, to a greater extent than tonic ESCS. At the single-session level, BCI-ESCS was followed by facilitation of MEP and PRM reflex

amplitudes, whereas tonic ESCS showed limited neurophysiological changes under matched conditions, underscoring the importance of volitional engagement to drive stimulation for neuromodulatory efficacy. These findings demonstrate that temporal coordination of exogenous spinal circuit activation with endogenous motor intent provides both immediate neuroprosthetic assistance and rapid facilitation of corticospinal and spinal excitability, supporting the potential of intent-driven neuromodulation to engage activity-dependent plasticity mechanisms.

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Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

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Program #/Poster #: PSTR094.18/W15

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Buoniconti Fund
Morton Cure Paralysis Fund

Title: BCI-driven Epidural Spinal Stimulation Drives Lasting Upper-Limb Recovery and Corticospinal Plasticity and After Chronic Tetraplegia

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Abstract: Spinal cord injury (SCI) disrupts corticospinal pathways and impairs voluntary movement, resulting in chronic paralysis and severely limiting independence and quality of life. Epidural spinal cord stimulation (ESCS) can modulate spinal sensorimotor circuits to facilitate motor output following SCI. Integrating ESCS with a brain-computer interface (BCI) that decodes volitional motor intent may further enhance recovery by aligning stimulation with attempted movement to drive activity-dependent neuroplasticity. Here, we present longitudinal

rehabilitation outcomes from three individuals with chronic cervical SCI (C3-C5 neurological levels; AIS A-D) who underwent a one-month BCI-controlled ESCS intervention. Percutaneous epidural spinal stimulation leads were implanted caudal to the injury targeting upper-limb sensorimotor circuits spanning C5-T1, and a BCI decoded motor imagery from electrocorticography (ECoG) signals to trigger ESCS during activity-based therapy, with a decoding success rate of 83.8±4.2%. Upper-limb function was assessed at Baseline, Endpoint, and one-month Follow-up after lead explantation using the TRI-HFT as the primary outcome, alongside GRASSP, reaching kinematics, and corticospinal excitability via motor evoked potentials (MEPs). Following the one-month intervention, all participants demonstrated meaningful functional improvements: the TRI-HFT 10-object manipulation task improved by an average of 17.3 points, exceeding the minimal detectable change of 9.1 points, GRASSP prehension scores increased by an average of 3.5 points, and reaching showed improved smoothness and endpoint accuracy. These functional gains were retained at one-month Follow-up without ongoing stimulation. At the neurophysiological level, MEP amplitudes were significantly facilitated at Endpoint across all participants, suggesting cumulative potentiation of corticospinal pathways through activity-dependent synaptic plasticity, though MEPs returned toward baseline at Follow-up. The persistence of functional gains despite this neurophysiological decline suggests that sustained recovery reflects contributions beyond corticospinal excitability alone. These findings support BCI-ESCS as a therapeutic neuromodulation approach that harnesses volitional intent to drive synaptic plasticity, promoting functional recovery following chronic cervical SCI and offering a promising new direction for motor restoration.

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Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.19/W16

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Wings for Life Project Grant WFL-CH-26/24
Gisela Hagemann Foundation

Title: Stimulation of the cuneifom nucleus to improve walking in patients with incomplete spinal cord injury

Authors: *A.-S. HOFER[1,2], L. FILLI[3,4], P. FREUND[3], M. E. SCHWAB[5], A. CURT[3], L. STIEGLITZ[2];
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Switzerland; [4]Swiss Paraplegic Res., Nottwil, Switzerland; [5]Inst. of Regenerative Med., Univ. of Zurich, Schlieren, Switzerland

Abstract: The mesencephalic locomotor region (MLR) modulates spinal locomotor circuits (central pattern generators, CPGs) via the reticulospinal tract. Following incomplete spinal cord injury (iSCI), reticulospinal input to lumbosacral CPGs is disrupted, contributing to impaired stepping ability and limited efficacy of gait training. Preclinical rodent studies have demonstrated that deep brain stimulation (DBS) of the cuneiform nucleus (CNF), a key component of the MLR, can enhance impaired motor drive and improve locomotor function after iSCI. Given the evolutionary conservation of the CNF-reticulospinal system, we hypothesize that CNF-DBS can similarly augment training and improve walking function in patients with iSCI. We thus initiated a clinical pilot trial (clinicaltrials.gov: NCT03053791, DBS-SCI trial), in which non-ambulatory patients with iSCI above T10 receive 6 months of gait training supported by personalized CNF-DBS (Stieglitz & Hofer et al., BMJ open, 2021). Participants undergo regular follow-up assessment of motor and non-motor functions without and with stimulation. The primary endpoint is a ≥30% improvement in walking distance in the 6-Minute Walking Test after 6 months relative to baseline. To date, all enrolled participants (n = 3) have tolerated both surgery and CNF-DBS without serious adverse events. Participant 1 achieved the primary study endpoint in the off-condition, and participant 2 in both the off- and the on-condition (Hofer & Stieglitz et al., Annals of Neurology, 2026). Accurate CNF targeting is critical due to its proximity to neighboring brainstem structures, yet human data on optimal stimulation sites remain limited. To address this challenge, we translated the functionally and anatomically defined stereotactic location of the rodent CNF to the human brain. This cross-species analysis yielded heuristic coordinates and anatomical landmarks (Hofer et al., Brain Stimulation, 2026) to guide electrode implantation in the third and future DBS-SCI trial participants. Participant 3 is currently undergoing CNF-DBS-supported gait training and has shown encouraging progress to date. Analysis of treatment-related effects on walking function as well as reticulospinal plasticity (StartReact paradigm) is currently ongoing.

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Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

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Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH R01-NS124224
New York State Department of Health C39070

Title: Individualizing paired stimulation parameters to induce neuromuscular plasticity in individuals with chronic cervical spinal cord injury

Authors: *C. N. SIGAFOSE[1], L. M. MURRAY[2], J. GOLDSMITH[1], T. SUTOR[1], F. CASTANO[1], D. ARNERO[1], M. LIU[1], J. R. MCINTOSH[3], J. B. CARMEL[4], N. Y. HAREL[5]; [1]Spinal Cord Damage Res. Ctr., Bronx, NY; [2]Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY, ; [3]Columbia Univ., New York, NY, ; [4]Columbia Univ. Med. Ctr., New York, NY, ; [5]Neurology; Rehabil. and Human Performance, James J. Peters Veterans Affairs Med. Ctr., Bronx, NY

Abstract: Background: Paired stimulation between the motor cortex and spinal cord sensory afferents targeting synapses in the spinal cord can augment the immediately ensuing motor evoked potential (MEP) (McIntosh et al. 2024; Murray et al. 2025), but there is limited information on how to best deliver repetitive stimuli in humans to induce lasting improvements in nerve transmission and motor function. In participants with chronic cervical SCI, we tested multiple parameters in an attempt to optimize lasting plasticity with repetitive paired stimuli. **Methods**: Participants with chronic (> 1 year) cervical SCI and partially spared hand or wrist function underwent repetitive stimulation with transcranial magnetic stimulation (TMS) over the motor cortex and/or subthreshold transcutaneous spinal cord stimulation (TSCS) over the cervicothoracic cord. Various repetitive stimulation parameters were tested in each participant: frequency, intensity, number of pulses, number of bouts, and incorporation of exercise. We attempted to optimize each parameter sequentially, then employed the best value in subsequent sessions while testing the next parameter. Primary outcomes were assessed as percent change from baseline up to 90 minutes following each intervention: target muscle MEP responses (physiological outcome); and performance on the Box and Block Test (BBT) of upper extremity dexterity (clinical outcome). **Results**: Pairing: to date, single-bout synchronized paired stimulation (suprathreshold TMS with subthreshold TSS) has been performed in 32 sessions across 8 participants. One bout of unpaired TMS has been performed in 11 sessions across 6 participants. One bout of unpaired TSS has been performed in 14 sessions across 7 participants. Post-intervention MEP responses have been facilitated by 39.0% ± 31.4%, 31.4% ± 20.4%, and 5.8% ± 9.5%, by paired stimulation, unpaired TSS, and unpaired TMS, respectively. Frequency: to date, single-bout intermittent 5 Hz paired stimulation has been performed in 19 sessions across 7 participants, whereas continuous 2 Hz paired stimulation has been performed in 13 sessions across 6 participants. Post-intervention MEP responses have been facilitated by 53.6% ± 40.3% and 19.0% ± 20.7% by intermittent 5 Hz and continuous 2 Hz, respectively. Across these 32 sessions, post-intervention BBT results have been facilitated 9.6% ± 5.2% and 10.3% ± 3.6% by intermittent 5 Hz and continuous 2 Hz, respectively. Data collection is ongoing and will be analyzed via multilevel linear modeling to account for variations in stimulus parameters.

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Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

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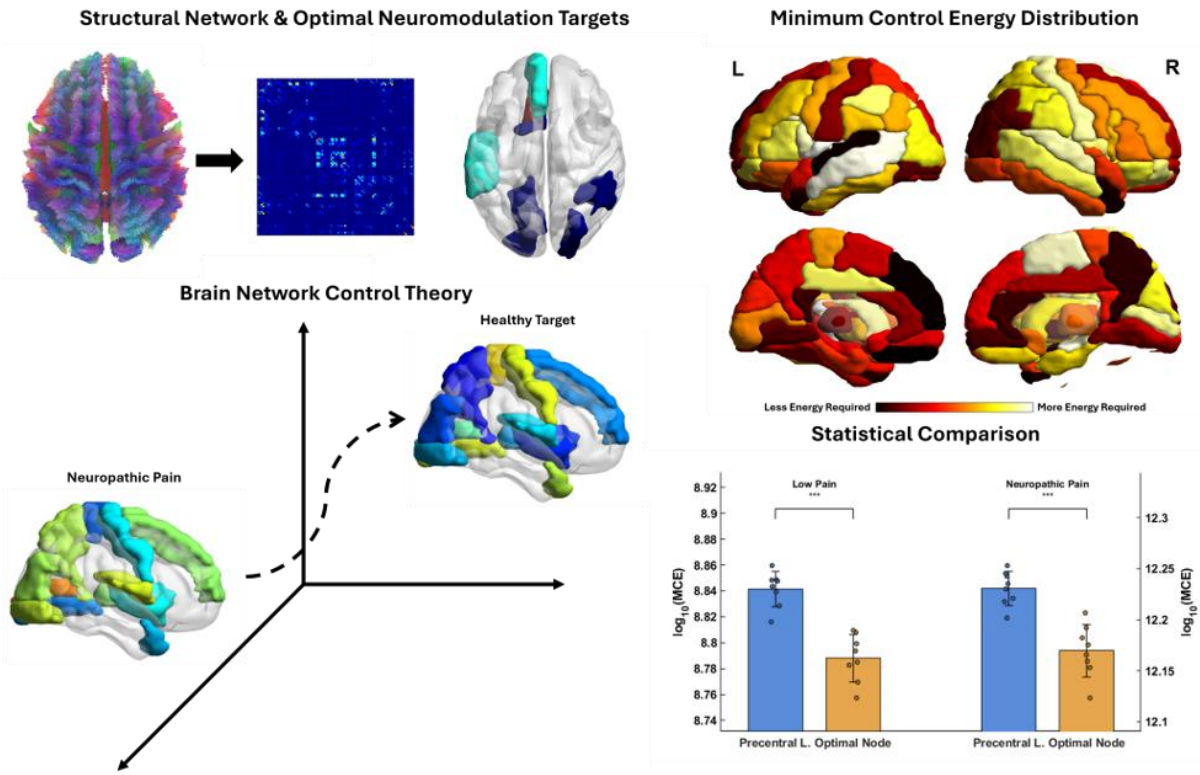
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Title: Personalizing neuromodulation targets for neuropathic pain in patients with spinal cord Injury with brain network control theory

Authors: *M. HOUSTON[1], C. LINNMAN[2], L. R. MORSE[2], Y. ZHANG[3];
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Abstract: Neuropathic pain is a prevalent and debilitating consequence after experiencing a spinal cord injury (SCI), with limited treatment options. Repetitive transcranial magnetic stimulation (rTMS) of the left precentral gyrus is emerging as a non-invasive, alternative treatment for neuropathic pain, but no framework currently exists for personalization of neuromodulation targets and validating whether the left precentral gyrus is indeed the optimal neuromodulation target. This preliminary study aims to identify patient-specific neuromodulation targets through brain network control theory (BNCT). Patients with SCI and severe neuropathic pain (n=8) and low-level pain (n=8) and age-matched non-injured controls (n=11) were recruited for this study. BNCT was applied to structural brain networks derived from diffusion tensor imaging. Resting state functional magnetic resonance imaging (rs-fMRI) was parcellated with the Automatic Anatomical Labelling (AAL) atlas and defined as the functional brain state. The minimum control energy (MCE) necessary to steer subject-specific brain states towards the group-average healthy control brain state was compared between the optimal control target (smallest MCE) and the left precentral gyrus in a 2-Way RANOVA with a horizon of T=100. Significant main effects of Group ($F(1, 7) = 637907.61$, $p < 0.001$, partial $\eta^2 = 1.00$) and Region ($F(1, 7) = 141.31$, $p < 0.001$, partial $\eta^2 = 0.953$) where identified. MCE was significantly lower for the optimal control target, frequently detected in the medial prefrontal cortex, versus the left precentral gyrus ($p<0.001$). The MCE necessary to transition to the healthy brain state was significantly lower in the low-pain group versus the neuropathic pain group ($p<0.001$). The results of this study suggest that the left precentral gyrus may not be the optimal neuromodulation target as evidenced by the lower energy requirements of other brain regions, highlighting the need for patient-specific targeted treatment in neuropathic pain conditions.



Disclosures: M. Houston: None. **C. Linnman:** None. **L.R. Morse:** None. **Y. Zhang:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.22/W19

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Buoniconti Fund to Cure Paralysis
Department of Health State of Florida

Title: Impaired Bilateral Locomotor Coordination After Incomplete Spinal Cord Injury Across Gait, Lower-Limb Motor Coordination, and Neuromuscular Synergies

Authors: *J. QUINTERO CONSUEGRA[1], Z. BOOGAART[1], H. SAITO[2], R. FADLI[1], A. SASAKI[3], A. YUASA[1], M. MILOSEVIC[4];
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Abstract: Restoring effective lower-limb function after spinal cord injury (SCI) requires not only improving overall motor capacity, but also understanding how injury disrupts the balance of function between the left and right sides of the body. Here, we evaluate whether individuals living with chronic, incomplete SCI demonstrate greater left-right functional asymmetry than able-bodied (AB) controls across overground walking, lower-limb motor coordination, and muscle synergy organization. Step length asymmetry (SLA) was calculated during the 10-meter walk test, and motor coordination was assessed with step count of each limb using the non-ambulatory lower-extremity motor coordination test (LEMOCOT). Surface electromyography was also recorded bilaterally during walking, and muscle synergies were extracted using non-negative matrix factorization to assess bilateral neuromuscular coordination patterns underlying gait. Consistent with impaired gait function, individuals with SCI walked significantly slower than AB controls and demonstrated reduced bilateral locomotor coordination, reflected by greater SLA during overground walking. In the complementary LEMOCOT, individuals with SCI displayed impaired lower-limb motor coordination and greater inter-limb asymmetry compared to AB controls. At the neuromuscular level, AB controls exhibited more distinct muscle synergy modules associated with phases of gait such as initial contact preparation, weight acceptance, and push-off, whereas individuals with SCI demonstrated reduced synergy complexity and merging of modules, particularly on the more affected side. Together, these findings suggest that locomotor impairment after SCI is characterized by deficits in bilateral locomotor coordination across biomechanical, behavioral, and neuromuscular domains. providing complementary markers of lateralized motor impairment.

Disclosures: J. Quintero Consuegra: None. **Z. Boogaart:** None. **H. Saito:** None. **R. Fadli:** None. **A. Sasaki:** None. **A. Yuasa:** None. **M. Milosevic:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.23/W20

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NYS Spinal Cord Injury Research Board Grant DOH01-C41212GM
NYS Spinal Cord Injury Research Board Grant DOH-C37714GG
Stratton VA Medical Center
James A. Eddy Memorial Foundation

Title: Usability and acceptance of robot-assisted sensorimotor training with neurophysiological recording in healthy volunteers

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Abstract: Introduction: Impaired somatosensation contributes to poor functional recovery following spinal cord injury (SCI), yet rehabilitation strategies remain predominantly motor-focused. To address this gap, we developed vibrotactile sensory discrimination tasks integrated into the Barrett Upper Extremity Robotic Trainer (Burt®) to enable robot-assisted sensorimotor training (RAST) combined with neurophysiological monitoring.
Methods: We conducted a feasibility and usability study in healthy volunteers (n=10), primarily rehabilitation therapists, to evaluate system integration and user acceptance prior to trials in individuals recovering from SCI. Participants completed one session of game-based active and passive upper extremity tasks incorporating structured vibrotactile cues. Tasks were designed to support sensory discrimination and event-related paradigms during concurrent measurement of electroencephalography-based brain signals and robot-based kinematics and vibration perception. Data was collected with informed consent, and the study was conducted under IRB #25-1121-4, Trinity Health New York Institutional Review Board.
Results: System usability was assessed using a 14-question survey with 2 open-ended questions, 12 Likert-scale survey questions (1=strong disagreement, 5=strong agreement), and an additional 10-question Likert active/passive task-specific survey. Participants reported high perceived usefulness (M=4.8, SD=.42), with strong agreement that sensory training is important for functional recovery (M=4.9, SD=.32) and accelerating rehabilitation (M=4.6, SD=.7). Integration into clinical workflows was rated favorably (M=4.8, SD=.42), with universal willingness to use the system clinically (M=4.9, SD=.32). Task-specific ratings across passive and active tasks indicated minimal fatigue (M=4.5, SD=.83) and high engagement (M=4.8, SD=.44), with slightly lower ratings for repetitiveness of the tasks (M=4.2, SD=.62). Qualitative feedback highlighted positive experiences with EEG comfort and overall usability, with suggestions for increased game variety and minor sensory parameter adjustments.
Conclusion: These results demonstrate usability, feasibility, and acceptance of robot-assisted sensorimotor training with integrated neurophysiological recording. This work establishes usability of a robust platform for evaluating the effects of RAST on cortical and neuromuscular function and informs trial design for comparing sensorimotor versus motor-only training in individuals with SCI.

Disclosures: A. Teale: A. Employment/Salary (full or part-time):; James A. Eddy Research Institute, Sunnyview Rehabilitation Hospital, Schenectady, NY. **C. McDonald:** A. Employment/Salary (full or part-time):; Barrett Technology, Newton, MA. **E. Mahan:** A. Employment/Salary (full or part-time):; Barrett Technology, Newton, MA. **W. Townsend:** A. Employment/Salary (full or part-time):; Barrett Technology, Newton, MA. **J. Hill:** A. Employment/Salary (full or part-time):; National Center for Adaptive Neurotechnologies, Stratton VA Medical Center, Albany, NY. Other; University at Albany, State University of New York, Electrical and Computer Engineering Department. **D. Gupta:** A. Employment/Salary (full or part-time):; National Center for Adaptive Neurotechnologies, Stratton VA Medical Center, Albany, NY. Other; University at Albany, State University of New York, Department of Electrical and Computer Engineering, Sunnyview Rehabilitation Hospital, Schenectady, NY.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.24/W21

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Kessler Foundation
Leona M. & Harry B. Helmsley Charitable Trust
University of Louisville Hospital
Christopher and Dana Reeve Foundation
Medtronic Plc

Title: Novel spinal sympathetic circuitry stabilizes blood pressure in chronic cervical spinal cord injury

Authors: *S. WANG[1], P. SHARMA[4], C. ANGELI[5], E. REJC[6], M. BOAKYE[2], B. UGILIWENEZA[3], J. WECHT[7], G. FORREST[5], S. HARKEMA[5];
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Abstract: Introduction: Spinal cord injury (SCI) causes severe dysregulation of hemodynamics, in addition to sensorimotor disability. Quality of life in the individuals with SCI is adversely impacted by unstable blood pressure (BP) including orthostatic hypotension, persistent hypotension and hypertensive episodes. Continuous spinal cord epidural stimulation (scES) at lumbosacral levels can stabilize BP in individuals with clinically-complete cervical SCI. This study explored the underlying mechanisms of this cardiovascular stabilization. **Methods:** Twelve participants with chronic clinically-motor complete cervical SCI and cardiovascular instability underwent implantation of a Medtronic neurostimulator (Intellis™) and a 16-electrode lead over the lumbosacral spinal segments. Electrical stimulation parameters were targeted to maintain seated systolic BP between 110-120 mmHg without evoking lower extremity muscle activity (CV-scES). After identifying CV-scES parameters, orthostatic tolerance was tested via a 70° head-up tilt for up to 30 minutes. Stability of systolic BP (SBP) over 6 hours in daily life was quantified by standard deviation of SBP (SD-SBP) and hypertensive deviation above 115 mmHg. CV-scES programs were compared to the stimulation parameters targeted for trunk stability (Vol-scES). One participant was tested with CV-scES on after taking an α_1-adrenergic antagonist (tamsulosin). Finally, the effects of spasticity on systolic BP were explored. **Results:** CV-scES significantly improved tilt duration when compared to stimulation off and Vol-scES. CV-scES also significantly reduced 6-hour SD-SBP and hypertensive deviation above 115 mmHg compared to stimulation off and Vol-scES. The stimulation programs targeting L4-L5 spinal level (based on distribution of cathodes) modulated BP more effectively than targeting higher lumbar levels. Tamsulosin attenuated the therapeutic effect of CV-scES. Spasms could cause BP elevation lasting a few minutes with stimulation off, which were attenuated and shortened with CV-scES and programs targeted to reduce unintended

muscle activity (MC-scES). **Conclusions:** Novel circuitry in the lower lumbar spinal levels can be stimulated to improve cardiovascular function. This effect can be attributed to the activation of sympathetic interneurons that project to α_1-adrenergic receptor on vascular smooth muscle. Hypertension is reduced by stimulation by targeting maladaptive pathways driving autonomic dysreflexia. Synergistically inhibiting unintended motor activation diminishes the rise in BP from spasticity.

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Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.25/W22

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Swiss National Science Foundation 32003B_208110
International Foundation for Research in Paraplegia P200

Title: Neuroplastic adaptations of descending motor pathways in individuals with chronic unilateral spinal cord injury (Brown-Séquard-plus syndrome)

Authors: A. M. EILFORT[1], L. C. NEUMANN[1], M. SCHUBERT[3], B. LAUBER[4], W. TAUBE[5], B. ZÖRNER[6], ***L. FILLI**[2,7];
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Abstract: Spinal cord injury (SCI) frequently causes sensorimotor impairments followed by partial spontaneous recovery. Neuroplastic reorganization of descending motor pathways is thought to be a key mechanism underlying functional recovery after SCI. Previous studies have demonstrated substantial plasticity within corticospinal and reticulospinal circuits following incomplete SCI. Here, we investigate motor system plasticity in individuals with chronic Brown-Séquard-plus syndrome (BSPS), a highly asymmetric SCI characterized by ipsilesional motor deficits and contralesional sensory impairments. BSPS provides a unique model for studying neuroplasticity, as one hemicord remains relatively preserved, while the other is largely disrupted. We enrolled four individuals with chronic, asymmetric unilateral spinal lesions consistent with BSPS, identified based on clinical examinations of motor and pinprick sensory asymmetry. These participants, along with four healthy controls, will soon undergo neurophysiological and clinical assessments. Functional recovery will be quantified using

clinical muscle strength measures, comparing acute (retrospective) and chronic time points. Quadriceps spasticity will be assessed using an instrumented pendulum test with inertial measurement unit (IMU) sensors. Descending motor drive will be evaluated bilaterally in the vastus medialis and tibialis anterior muscles. Reticulospinal and corticospinal function will be assessed using the StartReact paradigm and single-pulse transcranial magnetic stimulation (TMS), respectively. We expect substantial recovery of ipsilesional muscle function relative to the acute post-injury stage, accompanied by increased spasticity in the ipsilesional vastus medialis but little or no spasticity in the contralesional limb. Descending motor drive is expected to be initially reduced after SCI, particularly in the ipsilesional lumbar cord. Neuroplastic reorganization may alter the relative contributions of reticulospinal and corticospinal pathways to the denervated spinal cord. We hypothesize that reticulospinal plasticity will be most pronounced in the vastus medialis, a proximal muscle that receives strong reticulospinal input. In contrast, corticospinal drive is expected to be enhanced in the tibialis anterior, a distal muscle that relies heavily on corticospinal control. This study will explore neuroplasticity within the two principal descending motor systems in individuals with BSPS. The findings will provide insights into the respective roles of reticulospinal and corticospinal pathways in functional recovery and spasticity after incomplete SCI.

Disclosures: A.M. Eilfort: None. **L.C. Neumann:** None. **M. Schubert:** None. **B. Lauber:** None. **W. Taube:** None. **B. Zörner:** None. **L. Filli:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.26/W23

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: ONWARD Medical
Innosuisse
Study sponsor: École polytechnique fédérale de Lausanne (EPFL)

Title: ARC-IM Therapy to support and promote recovery of ambulatory functions in people with subacute and chronic spinal cord injury: A pilot study

Authors: *S. FUEREDER[1,2], C. FRAYSSINHES[3,5,6], G. CARPARELLI[3,5,6], N. HANKOV[3,5,6], M. FOURNIER[3,5], N. INTERING[3], C. DESCHENAUX[3,5], L. BOLE-FEYSOT[3,5], A. NIKOLAEVA[3,5], E. DAGHER[5,6], S. HERNANDEZ CHARPAK[3,5,6], S. DAETWYLER[3,6], P. FORERO[3,5,6], J.-B. LEDOUX[4,7], F. BECCE[4], S. ACHERMANN[1], M. JACOME[1,8], A.-S. HOFER[9,8], L. FILLI[1], L. ASBOTH[3,5,6], J. BLOCH[6,10,5], G. COURTINE[6,10,5], B. ZÖRNER[9]; [1]Swiss Paraplegic Res., Nottwil, Switzerland; [2]Sensory-Motor-Systems Lab., Swiss Federal Inst. of Technol. Zürich (ETHZ), Zürich, Switzerland; [4]Dept. of Diagnos. and Interventional Radiology, [3]Lausanne Univ. Hosp. (CHUV) and Univ. of Lausanne (UNIL), Lausanne,

Switzerland; [5].NeuroRestore, EPFL/CHUV/UNIL, Lausanne, Switzerland; [6]NeuroX Institute, Sch. of Life Sci., Ecole Polytechnique Fédérale de Lausanne (EPFL), Geneve, Switzerland; [7]Ctr. for BioMedical Imaging (CIBM), Lausanne, Switzerland; [8]Univ. of Lucerne (UniLU), Lucerne, Switzerland; [9]Swiss Paraplegic Ctr. (SPZ), Nottwil, Switzerland; [10]Dept. of Clin. Neurosci., Lausanne Univ. Hosp. (CHUV) and Univ. of Lausanne (UNIL),, Lausanne, Switzerland

Abstract: ARC^{IM} Therapy to support and promote recovery of ambulatory functionsin people with subacute and chronic spinal cord injury: A pilot study

Spinal cord injury (SCI) often results in severe motor deficits that impair mobility and quality of life. While rehabilitation augmented by epidural electrical stimulation (EES) of the lumbar spinal cord has improved ambulatory function in people with chronic SCI, whether delivering this intervention during the subacute phase further enhances recovery remains unknown. SCI creates a time-limited window for augmented nervous system reorganization that promotes spontaneous recovery, and we hypothesize that EES during this period may enhance neurological recovery. This ongoing two-center, non-randomized pilot study evaluates the safety, feasibility, and efficacy of ARC^{IM} Therapy, combining EES delivered through the ARC^{IM} Lumbar System with rehabilitation. Adults aged 18-65 years with traumatic SCI (AIS A-D, neurological level T10 or above) are enrolled in either the subacute (<6 weeks post-injury) or chronic (>1 year post-injury) phase. Twelve participants are planned for inclusion (n=6 per group). Safety is assessed through adverse events related to the procedure or therapy. Efficacy is evaluated through immediate stimulation effects and longitudinal changes in ambulatory performance using ISNCSCI, 10-Meter Walk Test, 6-Minute Walk Test, Timed Up and Go, and WISCI II. Recovery outcomes will be compared with matched historical controls. Differences between subacute and chronic participants will be explored to assess the influence of intervention timing on recovery. Additional outcomes include functional independence, quality of life, pain, neuromodulation measures, and feasibility of integrating ARC^{IM} Therapy into standard-of-care rehabilitation. Recruitment is ongoing. This study will provide first-in-human evidence regarding the safety, feasibility, and therapeutic potential of ARC^{IM} Therapy across different stages of SCI and inform future controlled trials aimed at improving walking recovery after SCI.



Disclosures: S. Fuereder: None. **C. Frayssinhes:** None. **G. Carparelli:** None. **N. Hankov:** None. **N. Intering:** None. **C. Deschenaux:** None. **L. Bole-Feysot:** None. **S. Hernandez Charpak:** None. **A. Hofer:** None. **L. Filli:** None. **L. Asboth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **J. Bloch:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. F. Consulting Fees (e.g., advisory boards); Consultant of ONWARD Medical. **G. Courtine:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. F. Consulting Fees (e.g., advisory boards); Consultant of ONWARD Medical. **B. Zörner:** None.

Poster

PSTR094: Spinal Cord Injury: Human Studies in Electrical Stimulation, Neuromodulation, and Brain Computer Interfaces

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR094.27/W24

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: UH3NS116238
Reynolds Foundation

Title: Distinct Frequency Signatures of Intermuscular Coherence Differentiate Voluntary from Stimulation-Induced Contractions in individuals with SCI

Authors: *C. A. ANGELI[1,3], G. F. FORREST[2,3], S. KIRSHBLUM[4,3], S. HARKEMA[1], M. BOAKYE[5];
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Abstract: Intermuscular coherence reflects frequency-specific common neural drive to motor neuron pools and offers a physiologically grounded approach to distinguish supraspinally mediated voluntary control from epidural stimulation-driven muscle activation in spinal cord injury. We compared the spectral organization of intermuscular coherence during voluntary and stimulation-induced contractions in individuals with thoracic motor complete spinal cord injury (SCI). Two participants (AIS-A) implanted with a 16-electrode epidural array over the lumbosacral spinal cord underwent systematic mapping to identify stimulation configurations enabling voluntary hip flexion (whole-leg flexion) at submotor threshold levels. Involuntary contractions were elicited by introducing parameter changes away from these configurations. EMG from iliopsoas and tibialis anterior was used to compute intermuscular coherence. Voluntary contractions exhibited a consistent multi-band coherence structure across individuals, characterized by strong low-frequency coherence (<5 Hz), a reproducible mid-frequency peak (~40-50 Hz), and coherence extending into higher-frequency (piper/gamma) ranges. This pattern is consistent with common corticospinal drive and coordinated supraspinal control. In contrast, involuntary contractions were dominated by low-frequency coherence and a limited number of narrow, frequency-specific peaks (~20-40 Hz), with minimal high-frequency coherence. The location of secondary peaks varied with stimulation parameters, suggesting parameter-dependent entrainment of spinal circuitry rather than stable cortical input. Within-subject comparisons revealed that involuntary contractions lacked the multi-band organization observed during voluntary control despite sharing strong low-frequency coherence. Instead, involuntary activity was characterized by sparse spectral structure and reduced high-frequency synchronization. Notably, involuntary patterns were more similar across individuals than to voluntary contractions within the same individual. These findings demonstrate that intermuscular coherence differentiates voluntary motor output from epidural stimulation-driven activation in SCI. The emergence of stable mid- and higher-frequency coherence appears to reflect supraspinal engagement, whereas low-frequency dominance with narrow peaks reflects stimulation-driven spinal network dynamics.

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Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.01/W25

Topic: E.03. The Chemical Senses

Support: Intramural NIH grant to M. Stopfer
Career development award to B. Song from NIH-NICHD

Title: A peripheral feedforward circuit amplifies taste signals, ensuring behavioral reliability.

Authors: *B.-M. SONG[1], M. A. STOPFER[2];
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Abstract: A fundamental challenge for nervous systems is ensuring that sensory signals reliably drive appropriate behaviors. While this reliability is typically attributed to processing in the brain, whether and how the sensory periphery itself contributes to reliable behavioral control remains poorly understood. Using *Drosophila*, a uniquely useful model for exploring peripheral taste circuits at the level of individual cells, we combined genetically driven transsynaptic mapping with paired simultaneous electrophysiological recordings. We revealed a functional, feedforward circuit comprised of similarly tuned bitter-sensing gustatory receptor neurons (GRNs). The circuit's synaptic connectivity is not all-to-all but selective, directional, and variable in strength. We identified the nicotinic acetylcholine receptor alpha 5 subunit as the primary mediator of inter-GRN synaptic transmission. Genetic ablation of the receptor abolished most inter-GRN interactions and destabilized taste-driven behavior, notably increasing behavioral variance without shifting response magnitude. Genetic cell-specific receptor rescue fully restored the circuit's functional interactions and behavioral reliability. These results suggest the circuit's specific role is ensuring reliability rather than simply amplifying responses.These results demonstrate that peripheral sensory neurons are not isolated transducers but rather work together to form distinct, synaptically connected circuits. Our work establishes synaptic computation at the sensory periphery as a previously unrecognized mechanism for reliable behavioral control. By combining transsynaptic mapping with paired recordings, our work also provides a proof-of-principle for comprehensive structural and functional analyses of peripheral sensory circuits that, together, provide an essential complement to connectomic approaches.

Disclosures: B. Song: None. **M.A. Stopfer:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.02/W26

Topic: E.03. The Chemical Senses

Support: Intramural Grant from NICHD

Title: Opposing signals converge in the fly gustatory system

Authors: *L. PAPPALARDO[1,2], M. A. STOPFER[1];
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Abstract: Neural mechanisms underlying taste remain unclear in any species, including humans. Two models exist: specific neurons and pathways are assigned to each taste (labeled lines), or taste is identified by activity patterns across groups of neurons (combinatorial coding). The fruit fly, *Drosophila melanogaster*, is a powerful model system that allows comprehensive experiments to elucidate gustatory mechanisms at the level of single, identifiable neurons.The labeled line model predicts that neural pathways representing distinct tastes should not converge. To test whether multiple first-order gustatory receptor neurons (GRNs) responding to different tastes converge onto a single second-order cell, we focused on the identified gustatory interneuron G2N-1. The recently published fly brain connectome revealed sugar-sensing (Gr64f), salt sensing (ppk23, vGlut), and water-sensing (ppk28) GRNs are presynaptic partners of G2N-1, and that some inputs to G2N-1 appear to be GABAergic. Using a genetically-driven tracing technique, BacTrace, we confirmed that sugar-sensing (Gr5a) and salt-sensing (ppk23,vGlut) neurons synapse onto G2N-1. We did not find evidence that water sensing (ppk28) neurons synapse onto G2N-1. We then expressed the fluorescent calcium indicator GCaMP6m in G2N-1 to monitor its activity during taste stimulation. G2N-1 responded consistently to sugars, but, despite BacTrace evidence of synaptic input from salt-sensing GRNs, G2N-1 showed no response to salts. GCaMP is not always an effective indicator of inhibition. We therefore hypothesize that G2N-1 is activated by sugary stimuli and inhibited by salty stimuli. To test this hypothesis and reveal how G2N-1 integrates excitatory and inhibitory signals, we are using patch-clamp electrophysiology to record its responses to taste delivery.The connectome shows that G2N-1 is part of a complex circuit; most of G2N-1's synaptic partners are other interneurons. To reveal how this combinatorial network processes taste, we are applying graph-theoretical approaches to model the gustatory system as a directed network, quantifying convergence, hub structure, modularity, and recurrent connectivity. Together, these studies will define how this interconnected network encodes tastes.

Disclosures: L. Pappalardo: None. **M.A. Stopfer:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.03/W27

Topic: E.03. The Chemical Senses

Support: NSF Grant 2332375

Title: Cross-connectome analysis predicts a sensorimotor circuit for protein taste in Drosophila.

Authors: *J. NEEFE, C. ARNTSEN, K. JOHNSON, R. ZIMMERMAN, M. STANLEY; Biol., Univ. of Vermont, Burlington, VT

Abstract: Organisms use chemosensation to guide their behavior and improve their survival. Specifically, taste allows an organism to evaluate its food, acting to promote the intake of

beneficial nutrients and suppress the intake of harmful substances. Amino acids are the building blocks of proteins, an essential nutrient for survival. Amino acid intake requires modulation as they are harmful both in deficiency and excess. The taste of amino acids is complex, eliciting appetitive and aversive signals in the nervous system and offering an important mode of feeding behavior modulation. It is not well understood how these complex signals are transformed into behavior. The model organism Drosophila melanogaster, commonly known as the fruit fly, allows us to study the neural circuitry involved in converting complex chemical stimuli such as amino acids into feeding behavior, a behavior relevant to all animals. Here, we identify an appetitive and aversive neural circuit for competing amino acid taste signals in two whole-brain connectomes in adult female Drosophila. Focusing on the neural circuit for the simple sensorimotor Proboscis Extension Response (PER), we used adjusted influence metrics to identify key neurons in each circuit, including a neuron called Pringle in the aversive circuit, which is predicted to be glutamatergic. We used in silico computational modeling to show that Pringle activation is necessary and sufficient to suppress motor output in the PER circuit and confirmed these results in vivo using a split-Gal4 genetic driver to target Pringle in the fly brain. Optogenetic activation of Pringle was sufficient to suppress PER to both sucrose and amino acids, confirming that it elicits an aversive signal. We also found that blocking synaptic output in Pringle increased PER to amino acids, suggesting that its activity is necessary to suppress PER. This work helps us to better understand the neural circuitry involved in converting chemical stimuli into feeding behavior, giving insight into how this necessary behavior is modulated by the nervous system.

Disclosures: J. Neefe: None. **C. Arntsen:** None. **K. Johnson:** None. **R. Zimmerman:** None. **M. Stanley:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.04/W28

Topic: E.03. The Chemical Senses

Support: NIGMS Grant R35GM142872

Title: Investigating the role of taste cells during parental care in a mouthbrooding cichlid fish

Authors: *M. LIAPIN[1], G. IGREJA ANDRÉ[2], S. A. JUNTTI[2];
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Abstract: Cichlid fishes are an emerging model in neuroscience to study the evolutionary, genetic, and hormonal bases of behavior. Among this family, *Astatotilapia burtoni* is an enticing model because of its genetic tractability and well-characterized mating behavior. While neural and hormonal underpinnings of courtship have been identified in this species, the mechanisms that promote subsequent parental care are virtually unknown. Most cichlid species, including *A.*

burtoni, hold offspring in their mouth for an extended period of time and forego feeding while fry develop. Although the brain areas associated with this mouthbrooding behavior are being investigated, little nothing is known about the sensory systems that promote this drastic form of parental care. Previous research indicates olfactory signals inhibit parental care in adult males in maternal-only care systems. In contrast, the sensory signals that drive the same behavior in females are unknown. As offspring constitutively interact with sensory neurons within a parent's mouth, we hypothesize a role of taste sensory neurons in maintaining parental care and suppressing any otherwise infanticidal feeding. To investigate whether taste sensory neurons are required, we target Type II taste cells. Type II taste cells respond to a majority of the five taste groups and utilize a conserved signal transduction pathway. To perturb this pathway we focus on PLCβ2, a phospholipase early in the pathway that has previously been shown to be required to discriminate sweet, bitter, and umami tastes in mouse studies. Using a CRISPR/Cas9 system, we generate *PLCβ2* mutant fish and quantify mouthbrooding success as well as taste preference compared to wild-type controls.

Disclosures: M. Liapin: None. **G. Igreja André:** None. **S.A. Juntti:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.05/W29

Topic: E.03. The Chemical Senses

Title: A phase-dependent model of synaptic remodeling during conditioned taste aversion

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Abstract: Conditioned taste aversion (CTA) is a conserved associative learning paradigm in which a novel taste becomes associated with visceral malaise, generating long-lasting avoidance. This model provides a valuable framework to examine how aversive memories are encoded, retrieved, and extinguished. The gustatory cortex (GC), basolateral amygdala (BLA), and central amygdala (CeA) participate in CTA; however, the molecular dynamics that distinguish acquisition, retrieval, and extinction remain only partially understood. Based on our previous and current findings, we propose a phase-dependent cortico-amygdalar model of synaptic remodeling mediated by growth-associated protein 43 (GAP-43) and synaptophysin (SYN). Previous acquisition data showed that aversive taste memory increased GAP-43 in the granular GC and enhanced SYN expression in GC, BLA, and CeA, suggesting that memory formation recruits both structural and presynaptic plasticity. In contrast, appetitive taste learning increased SYN without significant GAP-43 changes, indicating that taste memories of different valence engage distinct plasticity signatures. To extend this framework, male Wistar rats were subjected to

retrieval and extinction protocols. During retrieval, CTA animals showed reduced saccharin intake, confirming aversive memory expression. GAP-43 expression remained unchanged in GC and CeA, but significant differences were observed in BLA, where appetitive memory was associated with increased GAP-43 expression compared with control and CTA groups. These results suggest that retrieval-related remodeling may depend on taste valence rather than uniform reactivation of aversive circuits. During extinction, CTA and double CTA groups initially displayed reduced saccharin intake, followed by recovery of consumption across sessions. Double CTA animals showed increased GAP-43 expression in CeA and elevated SYN expression in CeA, with additional SYN differences in BLA. These results indicate that extinction of robust aversive memory recruits amygdalar structural and presynaptic remodeling. Together, our findings support a dynamic model in which acquisition engages GC-amygdala encoding mechanisms, retrieval involves BLA-dependent valence updating, and extinction requires CeA-centered plasticity associated with behavioral adaptation.

Disclosures: L.E. Grijalva: None. **E. Leon-Sarabia:** None. **R.G. Paredes:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.06/W30

Topic: E.03. The Chemical Senses

Support: R01DC022946

Title: Identifying the Mechanisms of Astringency Sensation

Authors: *M. MURPH[1], A. SEENAUTH[1], K. G. ESCOBAR[1], R. A. RAMOS[2], Y. MOAYEDI[1];
[1]Pain Res. Center, Mol. Pathobiology, NYU, New York, NY; [2]Hanna Gray Fellow, HHMI, Univ. of California, Berkeley, Berkeley, CA

Abstract: Astringency is defined as a dry, rough, and puckering sensation that is associated with the phenolic compounds that are present in many plant-based foods. Astringency sensation depends on the activation of trigeminal neurons, suggesting that transduction depends on somatosensation rather than taste. There is evidence that supports both chemosensory and mechanical modes of phenolic compound transduction, but the exact mechanism remains unknown. The goal of this study is to identify the cellular mechanisms by which trigeminal neurons transduce phenolic acids. Our preliminary *in vivo* calcium imaging findings show that trigeminal mechanosensory neurons that are responsive to tannic acid are responsive to stroking but not pressure, suggesting that astringency transduction occurs through mechanosensory neurons. We developed a method to measure behavioral aversion to tannic acid in olfactory- and taste-ablated animals using a brief access test. Our behavioral data indicates that neither Piezo 1 or 2 mediates tannic acid aversion, suggesting that mechanotransduction is not the primary

mechanism of transduction. Furthermore, we find that TRPV1 does not affect aversion. Using *ex vivo* calcium imaging to identify the response profiles of tannic acid responsive neurons, we found that tannic acid transduction occurs in the absence of mucosa and saliva. Additionally, tannic acid responsive neurons are further segregated into two subpopulations - one that selectively responds to tannic acid and one that overlaps with sanshool-responsive neurons, indicating transduction by the lingual correlates of K_2P expressing D-hair, Aδ-, or C- fibers. Collectively, our data indicates that astringency sensation is transduced by trigeminal mechanosensory neurons through chemosensory mechanisms, providing a potential mechanism of astringency aversion.

Disclosures: M. Murph: None. **A. Seenauth:** None. **K.G. Escobar:** None. **R.A. Ramos:** None. **Y. Moayedi:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.07/X1

Topic: E.03. The Chemical Senses

Support: Whitehall Foundation Research Grant
Mello Scholar Award
Startup funds

Title: A Peripheral Mechanism for Internal-State-Dependent Modulation of Salt Taste and Intake

Authors: L.-T. CHEN[1], X. XIA[2], E. SOTO[3], ***J. ZHANG**[4];
[1]UMass Med. Sch., Worcester, MA; [2]UMASS Chan Med. Sch., Worcester, MA; [4]Program in Mol. Med., [3]UMass Chan Med. Sch., Worcester, MA

Abstract: Sodium is an essential nutrient, and salt appetite provides a powerful model for understanding how physiological need alters taste perception and guides nutrient-specific appetites. Sodium depletion dramatically increases attraction to and consumption of salt in both animals and humans. While sodium depletion profoundly alters salt intake, how it influences salt taste remains unclear. Here we show that a tongue-secreted endothelin peptide modulates salt taste and intake. Under normal conditions, endothelin suppresses salt taste by acting on its receptor expressed on the peripheral projections of salt-sensing taste neurons. When internal sodium levels fall, tongue endothelin expression decreases, relieving this inhibition and enhancing neural and behavioral responses to salt. Applying endothelin to the tongue using a non-invasive gel-based delivery platform dampens salt-responsive neural activity and reduces salt intake. Conversely, genetic deletion of its receptor in taste neurons mimics sodium deficiency, increasing salt-responsive neural activity and salt consumption. Together, these

findings reveal a peripheral mechanism that regulates salt taste and intake in response to internal sodium status, highlighting a direct role of the taste system in maintaining nutrient homeostasis.

Disclosures: L. Chen: None. **X. Xia:** None. **J. Zhang:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.08/X2

Topic: E.03. The Chemical Senses

Support: NIH Grant R21DC022381-01

Title: Exploring the functional contribution of thalamus to dynamic computations in the gustatory cortex

Authors: *A. JORDAN[1,2], Y. STOILOVA[2], D. B. KATZ[3], S. D. VAN HOOSER[2];
[2]Biol., [3]Dept Psychol, [1]Brandeis Univ., Waltham, MA

Abstract: In many sensory modalities, the thalamus plays a key role in relaying and transforming sensory information to cortical regions through organized feedforward, feedback, and recurrent connections. While principles of thalamic processing and its spatial mapping in sensory cortices such as visual cortex are well-established, the functional role of the thalamus in the gustatory system is poorly understood. The goal of this research is to characterize the functional architecture and waveform signatures of thalamocortical inputs in the gustatory cortex during taste experience in anesthetized male and female Long-Evans rats. To resolve this, we have adapted an electrophysiological method that has been successful in the visual cortex (Sibille et al. 2024) —disentangling thalamic afferent activity from local cortical soma activity in the gustatory cortex using high density silicon electrodes. We recorded thalamic afferent and cortical activity simultaneously in the gustatory cortex using high density silicon probes while providing a battery of palatable and aversive tastes. The engineering of high density silicon electrodes allows for mapping of these thalamocortical signals across the gustatory cortex to determine if there are region or layer-specific physiological properties (responses latency, reliability, and transience/ sustainedness) or taste selectivity. The goal of our study of thalamocortical signals across the gustatory cortex is to set the groundwork for future studies that explore the role of thalamus in taste processing dynamics.
Sibille, J., Gehr, C., & Kremkow, J. (2024). Efficient mapping of the thalamocortical monosynaptic connectivity in vivo by tangential insertions of high-density electrodes in the cortex. Proceedings of the National Academy of Sciences, 121(4), e2313048121. https://doi.org/10.1073/pnas.2313048121

Disclosures: A. Jordan: None. **Y. Stoilova:** None. **D.B. Katz:** None. **S.D. Van Hooser:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.09/X3

Topic: E.03. The Chemical Senses

Support: NS120945
R37NS119012

Title: Valence-Based Ensemble Segregation of Sweet and Bitter Taste in the Rostral Nucleus of the Solitary Tract

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Abstract: Taste perception is critical for survival, promoting the ingestion of nutrients (sweet) and avoidance of toxins (bitter). At the periphery and in the gustatory cortex, these taste qualities are encoded by distinct receptor populations and represented by separate neuronal ensembles. Electrophysiological studies have shown that neurons in the rostral nucleus of the solitary tract (rNST) often respond to multiple taste modalities, with individual neurons exhibiting preferential responses to specific tastants. In contrast, Fos immunohistochemistry studies have suggested differential chemotopic organization of sweet- and bitter-responsive neurons within the rNST. However, it remains unclear whether taste qualities are represented by distinct neuronal ensembles at the cellular level. Specifically, we asked whether sweet and bitter stimuli are organized in the rNST as (1) spatially segregated neuronal ensembles and (2) molecularly distinct neuronal populations.To address these questions, we used TRAP2 mice to label neurons activated by taste stimulation. Animals were anesthetized to minimize descending cortical influences and allowed to stabilize for 1 h before lingual stimulation. Ninety minutes after the onset of a 30-min taste stimulation period, 4-hydroxytamoxifen was administered to label activated neurons. Animals were perfused 5 days later, and horizontal brainstem sections were processed for RNAscope or immunohistochemistry. P2X2-positive fibers were used as a marker of gustatory afferent input. Quinine hydrochloride (QHCl)-activated (TRAP+) neurons were concentrated particularly within the glossopharyngeal nerve terminal field in rNST, whereas sucrose-activated neurons were more broadly distributed throughout the rNST. TRAP+ neurons extended caudally beyond regions of dense P2X2 labeling, and sucrose stimulation recruited significantly more neurons than QHCl stimulation (mean ± SEM: QHCl, 117 ± 7.0 cells, n = 4; sucrose, 154 ± 9.6 cells, n = 4; p = 0.0286) in the caudal rNST. In addition, QHCl-activated neurons were observed in more dorsal sections than sucrose-activated neurons. The proportion of excitatory (VGlut2+) TRAP+ neurons was similar between QHCl (50%) and sucrose (55%) groups. In contrast, the proportion of inhibitory (GAD1+) TRAP+ neurons appeared higher following QHCl stimulation (40% vs. 24%). These findings suggest that sweet and bitter stimuli recruit partially segregated neuronal ensembles within the rNST that differ in their spatial

distribution and inhibitory circuit engagement, supporting an early representation of taste valence in the brainstem.

Disclosures: C. Sun: None. **E. Xie:** None. **L. Hans:** None. **V. Vashisht:** None. **Y. Chu:** None. **J. Kapur:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.10/X4

Topic: E.03. The Chemical Senses

Support: NIH/NIDCD R01DC022610
NSF-GRFP award 2234683

Title: Dissociable representations of anticipated taste and action in gustatory cortex during odor-evoked expectation

Authors: *A. GEORGE[1], A. FONTANINI[2];
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Abstract: In nature, animals often rely on non-gustatory cues, such as odors, to infer the identity of foods and select them for consumption. The gustatory cortex (GC) processes taste-related sensory signals, but recent evidence suggests it also participates in cognitive functions such as expectation and decision making. GC neurons modulate firing in response to auditory, visual, somatosensory, and olfactory cues predicting different tastes. However, it remains unknown how this anticipatory activity encodes taste-related variables (e.g., taste identity and action-predictive value) and guides ingestive behavior. To investigate these questions, we trained mice on a task in which pure odors and their mixtures predicted two palatable tastes. Mice were presented with a pure odorant ((+)- or (-)-limonene) or a mixture (70/30 or 30/70) followed by a brief delay, then required to make a directional lick. Mice were trained to associate the dominant odor with a lick direction and taste outcome, licking left to receive sucrose or right to receive monosodium glutamate (MSG). Optogenetic inhibition of GC during the delay between odor sampling and licking increased incorrect choices, demonstrating that GC contributes to odor-guided consumption decisions. Using high-density silicon probes, we recorded single-neuron activity during this task. Firing rate analysis revealed clear temporal dynamics in population activity. During odor sampling, GC produced patterns of activity that reflected the identity of the odor, while during the delay, showed anticipatory activity aligning with the animal's choice. To dissociate whether choice-related GC anticipatory activity reflects expected taste identity or lick direction, a second cohort of mice was trained on a task variant utilizing four distinct odors, providing cues for sucrose-left, water-left, water-right, and MSG-right. By comparing conditions sharing direction but differing in taste outcome (sucrose-left vs. water-left) or sharing outcome

but differing in direction (water-left vs. water-right), we disambiguated anticipatory activity selective for expected taste identity and lick direction. Neural representations were more distinct for conditions differing in both taste and direction than direction alone. When lick direction was held constant, responses to the sucrose-paired cue generalized to the taste of sucrose, but not to water, indicating taste identity is represented in GC activity during odor-evoked expectation. Together, these findings suggest GC neurons represent multiple variables during taste expectation, and anticipatory activity is directly related to the encoding of the taste itself.

Disclosures: A. George: None. **A. Fontanini:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.11/X5

Topic: E.03. The Chemical Senses

Support: NIH/NIDCD R01DC020722

Title: Gustatory cortical neurons expressing gastrin-releasing peptide modulate feeding

Authors: *D. GUARINO[1], J. CHEN[2], L. CZARNECKI[3], A. FONTANINI[4];
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Abstract: The gustatory cortex (GC) integrates sensory, limbic, and cognitive information to guide feeding in the context of the homeostatic state of the animal, yet the neurochemical mechanisms through which GC may contribute to regulating consumption remain poorly understood. Gastrin-releasing peptide (GRP) is a compelling candidate, as it is a neuropeptide whose central administration has been shown to suppress food intake in rodents. There is a notable population of GRP+ neurons in GC, suggesting a possible role for GC GRP+ neurons in shaping ingestion. However, whether and how GRP is implicated in cortical feeding circuits has yet to be explored. Here, we test the central hypothesis that GC GRP+ neurons are engaged by gustatory stimulation, and that manipulation of this population alters patterns of consumption. We used two-photon calcium imaging to test that GRP+ neurons are active in response to taste stimuli. We expressed GCaMP7f in animals who genetically express tdTomato in GRP+ neurons to identify potential differences in GRP+ and GRP- neural subpopulations. We found that GRP+ are indeed engaged by gustatory stimulation, with enhanced encoding of the meal replacement Ensure and other nutrients compared to GRP- neurons. To test the role of GRP+ neurons in feeding, we carried out two experiments. In the first experiment, GC GRP+ cells were selectively ablated and home-cage food consumption was monitored. We found that bilateral ablation of GC GRP+ via virally introduced caspase altered home-cage feeding behavior, with ablated mice showing a gradual increase in meal size over the course of three months. In the second

experiment, GC GRP+ were optogenetically activated and consumption of Ensure was monitored. Optogenetic stimulation of GC GRP+ during a 2-hour consumption task decreased overall intake of Ensure and altered licking microstructure in a way consistent with the notion that GRP acts as a satiety signal. Together, these studies uncover a novel role for GRP-producing neurons within GC and may reveal new insights into how sensory cortices guide feeding behavior.

Disclosures: D. Guarino: None. **J. Chen:** None. **L. Czarnecki:** None. **A. Fontanini:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.12/X6

Topic: E.03. The Chemical Senses

Support: OSU College of Dentistry Seed Grant
NIH - NIDCR T32DE 032994

Title: Taste exposure during a postnatal critical period impacts adulthood taste preference

Authors: *H. C. SCHIFF[1], E. CANTRELL[2];
[1]Ohio State Univ. Col. of Dent., Columbus, OH; [2]Neurosci. Grad. Program, Ohio State Univ., Columbus, OH

Abstract: Postnatal refinement of sensory cortical circuits contributes to perception, decision-making, and cognition, and these processes are modulated by sensory experience. We previously reported that taste experience at weaning influences sweet preference and cortical inhibition in gustatory cortex (GC), the primary sensory region for taste. These findings are consistent with human studies linking early taste experience to persistent effects on taste preference. Here, we test whether early life taste experience modifies preference across multiple taste modalities and homeostatic conditions and we examine the role of cortical experience-dependent plasticity of cortical inhibitory neurons in adult taste preference behavior. We first established a modified exposure paradigm in young mice (postnatal day P25-28) consisting of 4 days of 1 hour/day access to Ensure (as opposed to 8 days). During this period, mice exposed to Ensure consumed more than mice exposed to water, but body weight was not affected. This exposure paradigm was sufficient to enhance sucrose preference when mice were tested at P56 compared with control mice exposed only to water (water n=8, Ensure n=11 mice, $p<0.01$, F-test). Moreover, the increase persisted when a subset of mice were tested under sated conditions for their preference for sucrose (water n=6, Ensure n=8 mice, $p<0.05$, F-test). We next tested the role of cortical inhibition in sucrose preference with chemogenetic suppression of neural subpopulations in the gustatory cortex (GC), the primary sensory region for taste. We focused on parvalbumin-expressing (PV+) interneurons in GC because prior work has linked these cells and their associated perineuronal nets to experience-dependent refinement of cortical circuits, including

for GC. We found that chemogenetic suppression of PV+ interneurons in GC had opposing effects on taste preference when tested in the thirsty vs sated condition. Specifically, chemogenetic suppression reduced sucrose preference when tested thirsty and enhanced preference for a distinct palatable taste, Maltrin, when tested sated. Maltrin is a palatable, complex carbohydrate transduced independently of sweet taste receptors. Ongoing studies will determine whether this effect is specific to taste modality (sucrose vs Maltrin) or homeostatic state (thirsty vs sated). Ongoing efforts will determine whether experience-dependent plasticity of GC PV+ interneurons contributes to taste preference behavior in adult mice by assessing the effect of chemogenetic suppression of GC PV+ interneurons on taste preference in mice with early life Ensure exposure.

Disclosures: H.C. Schiff: None. **E. Cantrell:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.13/X7

Topic: E.03. The Chemical Senses

Support: Umami Research Grant 2025, Society for Research on Umami Taste, Japan
Toyoaki Overseas Travel Grant 2025, Toyoaki Scholarship Foundation
KAKENH 23K18257

Title: The NTS-CeL PKCδ pathway mediates suppression of aggression by MSG oral intake in an ADHD rat model

Authors: *D. MUSTIKA[1,2], S. TOMINAGA[1], M. SHINDO[1], H. HIDA[1];
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Abstract: Oral intake of monosodium glutamate (MSG) during the developmental phase reduces isolation-induced aggression in spontaneously hypertensive rats (SHR/Izm), which serve as a validated model for aggression in attention-deficit/hyperactivity disorder (ADHD). Nevertheless, the mechanisms involving the vagal and amygdalar circuits that underlie this behavioral effect are not yet fully elucidated. To address this, rats were housed individually from postnatal day 25 for a period of five weeks to induce aggression. During this time, they were provided with either water or a 60 mM MSG solution as their drinking fluid. Aggressive behavior was assessed using the resident-intruder test, followed by an immunohistochemical analysis of c-Fos expression. MSG administration significantly reduced the frequency and duration of aggressive grooming and attack behaviors and prolonged the latency to first attack compared to controls. Rats treated with MSG exhibited increased c-Fos expression in the intermediate nucleus of the solitary tract (iNTS) and the lateral central amygdala (CeL). Conversely, there was a decrease in c-Fos expression in the medial central amygdala (CeM), medial amygdala (MeA), and basolateral

amygdala (BLA), suggesting a region-specific modulation of amygdalar activity. Bilateral subdiaphragmatic vagotomy abolished both the anti-aggressive effects of MSG and the associated neural activation patterns, supporting a critical role of vagal signaling. To identify the relevant downstream pathway, acute intragastric MSG administration was combined with retrograde tracing from the CeA. MSG increased c-Fos expression in CeA-projecting iNTS neurons, whereas c-Fos expression in the parabrachial nucleus (PBN) was not significantly altered, suggesting that the direct iNTS-CeA projection, rather than the indirect iNTS-PBN-CeA pathway, is the major route involved. Furthermore, chemogenetic inhibition of the iNTS-CeA pathway using inhibitory DREADDs (hM4Di/CNO) abolished the anti-aggressive effects of MSG. Notably, both acute intragastric MSG administration and 5-week MSG ingestion followed by resident-intruder testing increased c-Fos expression in protein kinase C delta (PKCδ)-positive neurons in the CeL. These data demonstrate that MSG suppresses isolation-induced aggression through vagal activation of a direct iNTS-CeA circuit and selective recruitment of CeL PKCδ neurons. These findings reveal a vagally mediated gut-brain mechanism for the modulation of aggression-related amygdalar networks.

Disclosures: D. Mustika: None. **S. Tominaga:** None. **M. Shindo:** None. **H. Hida:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.14/X8

Topic: E.03. The Chemical Senses

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Research Funding for Longevity Sciences from the National Center for Geriatrics and Gerontology 25-29

Title: A novel mixture taste recall training improves mixture discrimination in healthy adults

Authors: *U. PARK, S. EBIHARA;
Dept. of Rehabil. Med., Tohoku Univ. Grad. Sch. of Med., Sendai, Japan

Abstract: Discrimination learning improves the ability to distinguish similar sensory stimuli through repeated experience. In taste perception, however, little is known about how training influences discrimination of complex taste mixtures that more closely resemble real-world food environments. Clarifying the perceptual characteristics of taste mixtures may provide insight into the mechanisms underlying taste discrimination learning. This study aimed to examine the discrimination characteristics of sweet-salty mixtures and changes in discrimination ability

following taste recall training. Forty subjects (20 each in the training and control groups) underwent sweet-salty mixture training, with taste thresholds for the four basic tastes (Sweetness, Saltiness, Sourness, Bitterness) measured before and after training. The sweet-salty mixture taste-recall training comprised four steps (1-4). In step 1, the mixture's taste threshold was measured. In step 2, the taste threshold of the mixture from step 1 and a concentration one level higher than the threshold were randomly presented, and training was repeated until recognition. In step 3, concentrations one level below and one level above the taste threshold were randomly presented, and training was repeated until recognition was achieved. In Step 4, the taste threshold and a concentration one level lower than the threshold were randomly presented, and training was repeated until recognition. Notably, the thresholds for both sweet and salty mixtures decreased with increasing training, indicating improved discrimination of mixed-taste stimuli. In contrast, thresholds for the four basic tastes remained unchanged following training. These findings suggest that improvements in mixed-taste discrimination cannot be fully explained by changes in basic taste sensitivity and may reflect distinct learning processes involved in the discrimination of complex taste mixtures.

Disclosures: U. Park: None. **S. Ebihara:** None.

Poster

PSTR095: Taste

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR095.15/X9

Topic: E.03. The Chemical Senses

Title: GLP-1 Receptor Agonists Significantly Impair Taste Function

Authors: *R. L. DOTY;
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Abstract: Over 10% of the US population are prescribed glucagon-like peptide-1 receptor agonists (GLP-1 RAs) to combat obesity. Although they decrease cravings for foods, their influence on chemosensory function is unknown. We employed state-of-the-art quantitative taste and smell tests to address this issue. The 53-item Waterless Empirical Taste Test (WETT®) and the 40-item University of Pennsylvania Smell Identification Test (UPSIT®) were completed by 46 persons taking GLP-1 RAs and 46 controls matched on age, sex, smoking behavior, and COVID-19 infection histories. Data were analyzed using analyses of variance. The WETT® scores were significantly diminished in the GLP-1 RA group relative to controls [total means (95% CIs) = 28.61 (25.66,31.56) and 40.63 (38.35,42.91), $p < 0.001$, $\eta 2 = 0.37$]. Eighty five percent of the GLP-1 subjects scored worse than their individually matched controls. All 5 WETT® subtest scores were similarly affected (ps < 0.001). Smell function, although slightly decreased on average, was not significantly impacted ($p = 0.076$). Women outperformed men on all tests. Remarkably, UPSIT® and WETT® scores were higher, i.e., better, in those reporting nausea, diarrhoea, and other GLP-1-related side effects. This study demonstrates, for the first

time, that GLP-1 RAs alter the function of a major sensory system, significantly depressing the perception of all five basic taste qualities. The physiologic basis of this effect is unknown but may involve GLP-1 receptors in the brainstem and afferent taste pathways, as well as vagus nerve-related processes.

Disclosures: R.L. Doty: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RLD president and major shareholder of Sensonics International, the manufacture and distributor of smell and taste tests, including the tests used in this study..

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.01/X10

Topic: E.05. Auditory and Vestibular Systems

Support: Pixie Dust Technologies, Inc.

Title: Effects of intra- and cross-modal interference stimuli on steady-state brain responses

Authors: *M. YONETAMARI[1], S. OTSUKA[2,3,4], Y. NAGATANI[6], T. HOSHI[6], S. NAKAGAWA[2,3,4,5];
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Abstract: Steady-state brain responses such as the auditory steady-state response (ASSR) and the steady-state visually evoked potential (SSVEP) are thought to be influenced by modulation filters that analyze temporal fluctuations in amplitude envelopes. However, most previous studies have used stimuli with a single modulation frequency, and studies using stimuli with multiple modulation frequencies remain limited. In this study, we investigated intra-modal and cross-modal interference effects on ASSRs.In the intra-modal experiment, ASSRs were measured in response to complex amplitude-modulated (AM) sounds with a 500-Hz carrier frequency; one modulation frequency was fixed at 40 Hz, and the other was varied from 11 to 39 Hz. For comparison, ASSRs elicited by single-frequency AM sounds with modulation frequencies ranging from 11 to 40 Hz were also measured. The levels of the individual frequency components were matched between the single-frequency and complex AM sounds. Compared with those elicited by the single-frequency AM sounds, ASSR peak amplitudes were significantly reduced at almost all frequencies in the complex AM conditions, suggesting that interfering modulation components compete for neural resources. Although the effects of the interfering frequencies on the 40-Hz ASSR amplitude were not statistically significant, amplitude reductions tended to occur around 15 and 27 Hz. According to a previously proposed modulation filter model, the bandwidth of a modulation filter above 10 Hz is approximately half

of its center frequency; however, the present results were not consistent with this prediction. Furthermore, ASSR amplitudes at the interfering modulation frequencies generally increased with frequency but showed a local decrease around 27 Hz. Because ASSR amplitudes elicited by single-frequency AM sounds are known to peak near 40 Hz, these results likely reflect the intrinsic modulation-frequency characteristics of the ASSR.In the cross-modal experiment, ASSRs elicited by a 40-Hz AM auditory stimulus were measured while visual flicker stimuli at 10 or 35 Hz were presented. Although no statistically significant differences were observed, ASSR peak amplitudes tended to be lower during simultaneous auditory-visual stimulation than during auditory-only stimulation. This finding suggests that competition for neural resources may also occur across sensory modalities, leading to cross-modal interference.

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Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.02/X11

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC018790
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Title: Functional organization of non-lemniscal thalamocortical inputs across mouse auditory cortical fields

Authors: *H.-J. SHIM, H.-K. LEE, P. O. KANOLD;
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Abstract: Non-lemniscal auditory thalamic pathways are thought to provide broad, higher-order input to the auditory cortex, but their bouton-level functional organization across auditory cortical fields remains unclear. Prior somatic recordings identified prominent offset-related responses in the non-lemniscal auditory thalamus (He, 2001, 2002), and cortical fields exhibit distinct temporal response patterns (Liu et al., 2019), raising the hypothesis that non-lemniscal projections provide an offset-dominant input channel to the auditory cortex. We examined the functional properties of these inputs in the superficial layers of mouse primary (A1) and

secondary (A2) auditory cortices, and tested whether they undergo cross-modal plasticity following short-term adult visual deprivation, a manipulation previously shown to potentiate lemniscal thalamocortical inputs (Petrus et al., 2014). We expressed axon-targeted GCaMP6s virus in the dorsal division of medial geniculate body (MGBd) of Calb2-IRES-Cre mice (10-12 weeks old; 7 males, 5 females; total n=12) and performed in vivo two-photon calcium imaging of superficial non-lemniscal thalamocortical boutons (40-50 μm depth) in awake mice during pure tone stimulation (4-64 kHz; 40, 55, 70 dB SPL). Using unsupervised k-means clustering, tone-responsive boutons were classified into prolonged-onset (OnP), transient-onset (OnT), offset (Off), and suppression-like classes. Contrary to an offset-dominant model, onset-responsive boutons formed the majority of the responsive population in both areas (OnP+OnT: 66.4% in A1, 63.6% in A2), while Off boutons accounted for 29.1% (A1) and 30.9% (A2). OnP boutons also showed the largest baseline-corrected peak ΔF/F amplitudes in both fields. Preferred-frequency (PF) maps revealed weak local spatial organization where boutons with diverse tuning were highly intermingled; local PF heterogeneity was high (~1.5 octaves) even within a 50 μm radius across all temporal classes. A1 and A2 shared strikingly similar class compositions, amplitude hierarchies, and broad frequency distributions. Finally, in a longitudinal subset (n=7), bilateral enucleation did not significantly alter the responsive bouton fraction, class composition, or response amplitudes one week later. These findings demonstrate that superficial non-lemniscal thalamocortical inputs deliver a temporally heterogeneous but predominantly onset-driven auditory signal that is broadly conserved across cortical fields and stable following short-term visual deprivation.

Disclosures: H. Shim: None. **H. Lee:** None. **P.O. Kanold:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR096.03/X12

Topic: E.05. Auditory and Vestibular Systems

Support: NIDCD F32DC020070

Title: Activity-dependent development in the mouse auditory brainstem

Authors: *R. TAING[1], L. J. KREEGER[2];
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Abstract: During postnatal development in mice,auditory brainstem circuits undergo physiological maturation to enable precise temporal processing. Prior to hearing onset, spontaneous hair cell activity shapes central pathways, while sound-evoked activity later refines the network. Octopus cells in the mammalian ventral cochlear nucleus are specialized for onset detection and submillisecond temporal processing of auditory inputs. They are sensitive to rapid membrane depolarizations, enabling coincidence detection of synchronous auditory nerve

activity. Their active properties depend on low input resistances, rapid time constants, and large hyperpolarization-activated and low-voltage-activated potassium conductances. That said, how octopus cells acquire such specialized computational properties remains poorly understood. We investigate the trajectory of octopus cell maturation and determine how early sensory experience shapes development. Here, we show that intrinsic membrane properties of octopus cells reach maturity by hearing onset (postnatal day 10-12).Whole-cell recordings from mouse cochlear nucleus slices reveal a rapid developmental transition between P4 and P12, during a period dominated by spontaneous activity. Across this interval, input resistance and time constant decreased roughly threefold and fivefold, respectively, while action potentials narrowed by nearly twofold. In parallel, octopus cells developed increased sensitivity to rapidly rising depolarizations, consistent with maturation of temporal coincidence detection mechanisms. To determine whether sound-evoked activity is required for this developmental trajectory, we examined octopus cells in two congenital deafness models: *Pcdh15*^{R245X} point mutation (protocadherin-15) and *VGlut3* (Vesicular glutamate transporter 3) knockout mice (Peters et al.,2023;Seal et al., 2008). After hearing onset, octopus cells from deaf mice exhibited increased excitability and elevated spike counts. However, membrane properties remained unchanged. Principal component analysis reveals a significant shift in the maturation trajectory of deaf octopus cells, suggesting that evoked auditory activity contributes to the early maturation program. Together, these findings identify a pre-hearing developmental window during which octopus cell intrinsic properties emerge, followed by a window during which sound-evoked activity refines temporal and spike properties. More broadly, these results reveal distinct phases of auditory brainstem maturation and provide insight into how congenital deafness alters the emergence of mechanisms underlying temporal processing.

Disclosures: R. Taing: None. **L.J. Kreeger:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.04/X13

Topic: E.05. Auditory and Vestibular Systems

Title: Neural Signatures of Auditory Expectation During Pattern Tracking

Authors: *E. A. CHUNG[1], S. NAYAK[2], E. S. SUSSMAN[1,3];
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Abstract: This study examined predictive coding mechanisms in auditory expectation formation, focusing on how expectations build through pattern tracking. The human brain excels at detecting environmental regularities; however, it remains unclear how patterns are extracted, maintained in memory, and influenced by attention. We investigated how stimulus-driven factors (implicit) and attention-based factors (explicit) modulate auditory pattern tracking. Neural

responses to sound patterns separated by silent intervals were compared with isochronous sequences. We hypothesized pattern tracking would be enhanced by explicit knowledge and stimulus-driven cues would strengthen tracking, reflected in the contingent negative variation (CNV) component of event-related potentials (ERPs).
14 healthy young adults (M = 24.1, SD = 1.2) completed four randomized conditions: Oddball Active, Oddball Passive, Train Active, and Train Passive. Auditory stimuli were presented in trains of nine tones (415 ms SOA), totaling 225 stimuli per run. Train conditions included a random 1-2 s inter-train interval, whereas oddball conditions were continuous. Novel tones engaged attention. Participants watched a closed-captioned movie during passive conditions and responded to novel tones in active conditions. EEG data were recorded, converted into ERPs, and analyzed using time-frequency methods to assess theta, alpha, and delta oscillations. Preliminary results revealed pattern tracking in both active and passive conditions, with stronger responses during active listening. Scalp topographies showed fronto-central activity to the first tone that decreased across successive tones, followed by a more occipital distribution associated with the CNV. Ongoing analyses will further characterize the effects of attention and stimulus structure on auditory expectation formation. Automatic auditory pattern tracking was indicated by the CNV-related activity observed during passive listening. These findings demonstrate real-time pattern tracking beyond deviance detection and a potential framework for quantifying predictive mechanisms in auditory cognition.

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Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.05/X14

Topic: E.05. Auditory and Vestibular Systems

Support: Z01 DC000091

Title: Physiology of the cochlear nucleus small cell cap

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Abstract: The small cell cap (SCC) is a region within the cochlear nucleus located between the dorsal and ventral cochlear nuclei. The neurons in this region receive exclusively high threshold, low-spontaneous rate auditory nerve fibers and are thought to project to medial olivocochlear neurons, which are involved in cochlear gain control. MOC neurons provide reciprocal cholinergic inputs. In vivo recordings of sound driven responses in neurons revealed that they encode amplitude modulations with high fidelity. However, it isn’t clear what role the SCC plays in auditory function. We used patch clamp electrophysiology to explore the intrinsic properties

of these neurons and better understand their role in auditory brainstem circuits.We generated a Penk-IRES-Cre;tdTomato mouse line for fluorescent labeling of SCC neurons. We then performed patch clamp electrophysiology recordings on individual penk+ neurons in sagittal brain slices. Cells were identified by their proximity to dorsal cochlear nucleus vertical cells, which are also labeled by penk. We found that SCC cells are spontaneously active, with two distinct patterns of discharge activity in the population- bursting and non-bursting. Voltage clamp recordings revealed different kinetics of outward currents that correlated with the distinct spontaneous activity patterns. Using a K means clustering approach on spiking and voltage clamp data reveals at least 2 subtypes of penk+ SCC neurons. It is unclear what the intrinsic differences are that contribute to response types or if there are separate functions of these cell types.Current clamp recordings found that SCC neurons produced spikes that quickly developed depolarization block when currents were above 70 pA. SCC cells have a low rheobase and a high input resistance, indicating that these neurons are highly responsive to inputs. Hyperpolarizing steps revealed a large Ih current and caused rebound spikes upon repolarization. ZD7288 blocked the Ih current and prevented rebound spiking, however it did not alter the input resistance, indicating an Ih activation range below the neuron's resting membrane voltage.Additionally, we tested the effects of efferent cholinergic inputs to SCC by applying 1mM acetylcholine and found that it strongly excited SCC neurons, increasing their spontaneous firing rate.Future experiments will identify the neuronal targets of SCC and the functions of SCC synapses.

Disclosures: J.F. Baldassano: None. **C.J. Weisz:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR096.06/X15

Topic: E.05. Auditory and Vestibular Systems

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Title: Auditory cortex a specialized hub for integrating crossmodal event boundaries

Authors: *J. BIGELOW[1], T. SUZUKI[2], A. R. HASENSTAUB[2];
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Abstract: Navigating a dynamic multisensory environment requires the brain to segment continuous sensory streams into discrete events. Most models of sensory processing emphasize the detection of stimulus onsets, and studies of the neural mechanisms of multisensory integration almost exclusively measure transient or sustained responses to the onset of sensory stimuli, leaving the neural mechanisms that signal stimulus terminations (offsets) poorly characterized. This is a crucial gap, as offset responses are essential for parsing speech, detecting silent gaps, and defining object duration. Given that the primary auditory cortex (AC) is heavily involved in both auditory offset signaling and crossmodal integration, we hypothesized that single neurons in AC might support multimodal event boundary detection. To test this possibility, we compared responses to the onsets and offsets of auditory, visual, and audiovisual stimuli in primary auditory and visual cortices. We recorded using high-density extracellular recordings (Neuropixels) in awake mice exposed to temporally dynamic auditory stimuli (e.g. windowed noise) and visual stimuli (e.g. contrast-modulated noise or full-field luminance changes) comprising interspersed “on” and “off” periods of varying durations. These data indicate a striking functional specialization: AC neurons were far more likely to fire at the offsets of visual stimuli than to their onsets, while VC neurons did not encode offsets in either modality. Visual offset-responsive units were found throughout the depths of AC, in contrast to visual onset-responsive units, which are concentrated in deep layers. This functional architecture persisted across both visual flash and contrast-modulated noise stimuli. Assessing cross-modal convergence revealed that visual offset-responsive neurons in AC show significantly stronger sound-offset responses than the general population. Crucially, simultaneous audiovisual offsets often evoked responses significantly larger than the linear sum of unimodal inputs, demonstrating non-linear cross-modal facilitation. This supra-linear integration even recruited units lacking direct unimodal visual responses. By contrast, the primary visual cortex (V1) lacked robust offset responses to these same temporal boundaries. These findings demonstrate a fundamental asymmetry in cortical processing, and imply that the AC may be a specialized, multisensory hub for computing environmental termination signals, integrating cross-modal cues to form a unified representation of event ending.

Disclosures: J. Bigelow: None. **T. Suzuki:** None. **A.R. Hasenstaub:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.07/X16

Topic: E.05. Auditory and Vestibular Systems

Title: Modeling the Auditory Steady-State Response with a Linear Damped Driven Oscillator

Authors: *K. M. SPENCER;
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Abstract: The auditory steady-state response (ASSR) of the electroencephalogram is evoked by the presentation of repetitive auditory stimuli, such as trains of clicks. In humans, the ASSR is maximal for stimulation frequencies around 40 Hz, suggesting that 40 Hz is the resonant frequency of the auditory system. In schizophrenia (SZ) the 40 Hz ASSR is reduced, which is thought to reflect dysfunction in a cortical circuit that generates gamma oscillations. Here I examined whether aspects of the ASSR and its impairment in SZ could be accounted for by a simple model of a damped and driven linear oscillator. The oscillator was described by the set of equations: 1) dx/dt = y, and 2) dy/dt = -b*y - (F_n^2)*x + S(F_{ext}), where x and y were the output in Cartesian coordinates, b was the damping force parameter, F_n was the natural frequency of the oscillator (set to 40 Hz), and S was the external driving stimulus at driving frequency F_{ext}. These equations were integrated using the Euler method (.0001 ms time step) and the output was sampled at 1000 Hz. The modulation transfer function (MTF) was used to represent the response of the oscillator to different stimulation frequencies. When the driving stimulus was a 40 Hz train of 1 ms pulses (click train), it introduced harmonics to the model ASSR, including a 40 Hz harmonic to 20 Hz stimulation that had a larger amplitude than the 20 Hz ASSR. Adding the damping force caused the time course of the ASSR to "ramp up" to the steady-state amplitude and to decay to zero after the stimulus ended. An initial transient 40 Hz response was produced by the first click in each train, regardless of the stimulation frequency. Finally, removing one click from the click train caused the ASSR to "reset", ramping up again to reach the steady-state amplitude. These phenomena are all characteristic of actual ASSRs in humans. Further increasing the damping parameter shifted the MTF downwards, such that there was no longer a clear 40 Hz maximum in the MTF, but at 30 Hz the MTF still overlapped the MTF of the "control" model. The time course of the model and initial 40 Hz transient were still preserved. Hence, the 40 Hz ASSR deficit in SZ can be modeled as an increase in the damping force, which flattens the shape of the MTF. Thus, several aspects of the ASSR can be modeled by the damped and driven linear oscillator, including its time course, response to perturbation, and dysfunction in SZ. Estimation of the damping parameter in ASSR data might provide a better measure of gamma dysfunction in individuals with SZ than measuring 40 Hz power or phase locking. If so, identifying the neurophysiological correlates of the damping force could help pinpoint the circuit dysfunction that underlies the 40 Hz ASSR deficit in SZ.

Disclosures: K.M. Spencer: None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.08/X17

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC016599
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Title: The spectrotemporal features of sound are mapped through a novel cellular organization on the dorsal cortex of the mouse auditory midbrain.

Authors: *B. A. IBRAHIM[1], G. XIAO[2], S. SINGH[3], Y. SHINAGAWA[4], A. DOUGLAS[5], C. GLICK[6], D. LLANO[7];
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Abstract: The spectrotemporal features of sound are mapped through a novel cellular organization on the dorsal cortex of the mouse auditory midbrain. Baher A. Ibrahim[1,2], Gang Xiao[1,2], Simran Singh[1,2,3], Yoshitaka Shinagawa[4], Austin Douglas [6], Colin David Glick[4], Ebraheem Yaghmour[4] & Daniel A. Llano[1,2,3,4,5]1- Department of Molecular & Integrative Physiology, University of Illinois at Urbana-Champaign, IL, USA.2- Beckman Institute for Advanced Science & Technology, University of Illinois at Urbana-Champaign, IL, USA.3- Neuroscience Program, University of Illinois at Urbana-Champaign, IL, USA.4- School of Molecular & Cell Biology, University of Illinois at Urbana-Champaign, IL, USA.5- Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, United States, IL, USA.6- Dept of Statistics, University of Illinois at Urbana-Champaign, United States, IL, USA.Corresponding author: Daniel A. LlanoEmail: d-llano@illinois.edu
AbstractThe inferior colliculus (IC) serves as a central hub for auditory processing, receiving diverse ascending and descending projections. Most of the descending corticofugal projections terminate on its dorsal and lateral surfaces. The dorsal surface of the IC exhibits a reversal of tonotopic organization, thereby indicating the existence of multiple zones dedicated to processing different sound features that can be modulated by higher centers. The spectrotemporal properties of the dorsal surface of the IC were mapped using two-photon imaging of calcium signals, revealing regions that are both functionally and anatomically distinct. Along most medial and lateral regions of the surface, the dorsal (DC) and lateral cortices (LC) are located. While both regions are tuned to high sound and modulation frequencies, LC demonstrates characteristic GABAergic properties and has inputs and outputs that differ from those of DC. The DC and LC are clearly separated by a middle caudorostral area, which is tuned to lower sound frequencies, with 0 Hz representing the best modulation frequency. The three regions show shifts in their spectrotemporal preferences as a function of sound amplitude. Furthermore, cortical inhibition was observed to reduce spectrotemporal tuning across the mediolateral axis of the dorsal surface. These findings suggest that the dorsal surface of the IC comprises multiple zones that process sound features differently and are modulated by the corticofugal system.

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Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.09/X18

Topic: E.05. Auditory and Vestibular Systems

Support: SERB-CRG/2021/005653
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Title: Developmental alteration of auditory oddball selectivity in valproic acid induced autistic mouse model

Authors: *R. PURKAIT[1], S. BANDYOPADHYAY[2];
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Abstract: Altered sensory processing is common in autism spectrum disorder(ASD), but how atypical neurodevelopment changes cortical novelty detection across age, sex, and lamina remains unclear. We examined whether prenatal valproic acid(VPA) exposure causes developmental alterations in oddball selectivity within subplate neurones(SPNs) and layer4(L4) of mouse auditory cortex compared to age matched saline controls. These layers are central to the developmental emergence of auditory deviant detection and thalamocortical circuit maturation before and after ear canal opening(ECO).In adult , layer6b was also examined because it represents the developmental remnant of the subplate. Pregnant mice received VPA(400 mg/kg, i.p.) or saline at embryonic day 11.5-12.5. Extracellular single unit recordings were obtained from male and female offsprings of VPA treated (n=29; 2009 units) and saline treated mice (n=33 ; 3083 units) starting from critical period(CP) till adulthood at postnatal days (P)14-15 (CP), P16-20, P21-28, >P28. Paired oddball sequences with swapped standard/deviant frequency tones were used as stimulus paradigm. Deviant detection was quantified by common selectivity index(CSI) using mean standard response preceding deviant, first standard [CSI(F)] or pre-deviant standard [CSI(P)]; adaptation was estimated from exponential fit to repeated standard responses before and after the deviant. Control mice showed stronger deviant selectivity than VPA mice across development.CSI was higher in control across all ages, with the largest reduction in VPA at P16-20 and >P28. CSI(F) and CSI(P) confirmed reduced selectivity from P16-20 onwards. VPA treated females showed reduced deviant selectivity across all ages compared to control irrespective of cortical layers, whereas males showed age dependent and mixed treatment effects. VPA showed higher oddball selectivity at CP in L4 but lower at adulthood in both layers. Layer dependent CSI differences were also age and treatment specific, with saline CSI(F) generally higher in L4 than SP after CP, whereas VPA showed less consistent laminar patterns, including L4>SP during CP for CSI(F) and SP>L4 at P16-20 for CSI. Adaptation dynamics also depended on sequence position: before the deviant, L4 had larger adaptation time constant than SP/layer6b irrespective of age and treatment, whereas after deviant, SP/layer6b often showed larger time constant. These findings indicate that developmental VPA exposure weakens auditory cortical novelty detection and reorganizes adaptation in a sex, age, and layer dependent manner**,** supporting altered maturation of sensory predictive circuits in VPA induced autism model.

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Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

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Title: Characterization of the Auditory Steady State Response with intracranial EEG

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Abstract: Background. The auditory steady-state response (ASSR) is an auditory evoked response characterized by oscillations entrained to periodic stimuli. Maximal entrainment to the 40 Hz ASSR has been robustly recorded in adult humans across multiple extracranial methods, primarily scalp electroencephalography (EEG) and magnetoencephalography (MEG). However, due to the limitations of these recording methods, the exact neural circuitry underlying ASSR remains unknown. Here, we present the first characterization of the 40 Hz ASSR using intracranial EEG (iEEG). We hypothesize that the ASSR reflects bottom-up encoding of sensory information and predict that ASSRs propagate along the ascending auditory pathway.
Methods. Data was recorded in 14 neurosurgical patients undergoing clinical monitoring using stereotactic EEG (SEEG), with clinical neuroimaging for precise electrode localization. To elicit ASSRs, 500 ms click trains at 40 Hz were embedded into an auditory oddball task. We characterized the temporal and spatial characteristics of power and inter-trial phase coherence at 40 Hz during auditory stimulation. These metrics were compared across brain regions defined by within-subject anatomical parcellation.
Results. Out of 2,244 electrodes across all participants, 329 electrodes demonstrated increased power and phase coherence at 40 Hz following auditory stimulation. These electrodes spanned both cortical and subcortical areas, including auditory cortex and thalamus. ASSRs with the highest peak power were recorded in the temporal operculum, insula, temporal gyrus, inferior temporal gyrus, and transverse temporal gyrus. Pairwise statistical testing revealed significant differences in onset latencies between regions ($p<0.001$ for all pairs). Response onset latencies suggest a temporal propagation of ASSR responses starting in transverse temporal gyrus and temporal operculum, followed by insular cortex and culminating in supramarginal gyrus and superior temporal sulcus.
Conclusions. Localization of the ASSR network is a first critical step for understanding the clinical and research implications of this response. These findings represent the first intracranial characterization of 40 Hz ASSRs in humans. The variance in onset latency and power across

different anatomical regions suggests that ASSR can be used to map connectivity along the auditory pathway.

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Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

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Topic: E.05. Auditory and Vestibular Systems

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Title: Attention-Dependent Feature Subspaces for Population Encoding of Temporal Coherence in Auditory Cortex

Authors: *K. YU[1], H. K. SRIVASTAVA[2], J. M. FINE[3], B. Y. HAYDEN[5], K. JASPE[4], N. SCARCELLI[4], H. JIANG[4], J. A. HENNIG[6], M. J. MCGINLEY[1];
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Abstract: Temporal coherence (TC) between frequency channels helps listeners segregate target sounds from background noise. Attention supports this process by enhancing behaviorally relevant acoustic structure. In a mouse sustained-attention task, task utility improves detection of TC embedded in tone clouds (de Gee et al., 2024), but how auditory cortex (ACtx) represents TC at the population level, and how attention reorganizes this representation, remain unclear.We recorded ACtx activity while mice detected TC under fluctuating utility. Spectrotemporal receptive field (STRF) models (Huang et al., 2021) separated STRF-explainable neurons from neurons less well captured by low-level spectrotemporal features. STRF predictability decreased during TC stimuli, especially under high utility. Population CNN encoders identified a “complex acoustic” subpopulation better explained by nonlinear features than by STRFs. Linear decoding and tensor component analysis showed that TC decodability improved under high utility and was supported by distinct temporal and feature-related population structure. Reinforcement-learning RNN models trained on the TC task similarly developed deeper-layer units encoding coherence-related information not explained by STRFs.These results suggest that attention-dependent TC encoding depends on a nonlinear population feature subspace beyond classical STRF-like representations. Ongoing work will quantify this subspace using population encoders that map spectrotemporal inputs to ACtx spiking. We will identify feature axes, estimate dimensionality, and test whether TC representations emerge compositionally from simpler spectral and temporal

components, as proposed by object models based on coherent modulation of continuity, pitch, and spectral grouping (Krishnan et al., 2014). We will also incorporate task utility and pupil-indexed arousal as state inputs to determine how attention reweights or realigns the TC-coding subspace. This framework will study whether state-dependent changes in feature geometry explain improved TC detection and how internal state reshapes cortical population codes of TC. de Gee, J.W. et al. (2024). Strategic stabilization of arousal boosts sustained attention. Current Biology. Krishnan, L., Elhilali, M., & Shamma, S. (2014). Segregating complex sound sources through temporal coherence. PLoS Computational Biology. Huang, Z., Ran, Y., Oesterle, J., Euler, T., & Berens, P. (2021). Estimating smooth and sparse neural receptive fields with a flexible spline basis. bioRxiv.

Disclosures: K. Yu: None. **H.K. Srivastava:** None. **J.M. Fine:** None. **B.Y. Hayden:** None. **K. Jaspe:** None. **N. Scarcelli:** None. **H. Jiang:** None. **J.A. Hennig:** None. **M.J. McGinley:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.13/X21

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01 DC 019348

Title: Optogenetic Dissection of the Auditory Contralateral Tectothalamic Pathways

Authors: *J. A. KARA[1], T. VAUGHN[2], C. C. LEE[3];
[1]Louisiana state university, Baton Rouge, LA; [2]NeuroToxicology, Louisiana State Univ., Baton Rouge, LA; [3]Comparative Biomed. Sci., LSU Sch. of Vet. Med., Baton Rouge, LA

Abstract: The medial geniculate body (MGB) receives diverse and robust ascending and descending projections, making it a critical hub in the central auditory system. Both ascending excitatory and inhibitory inputs to the MGB originate from the auditory midbrain (inferior colliculus: IC) which conveys and regulates auditory signals. Although the ipsilateral tecthothalamic pathways serve as the primary ascending driver input on the MGB neurons, the contribution on the contralateral tectothalamic pathways remain unclear, particularly regarding how their inputs shapes the MGB neurons responses to acoustic stimuli. Therefore, to investigate the unexplored functional role of the contralateral tectothalamic pathways, we employed cell-type specific, *in vivo* optogenetic electrophysiological experiments to delineate the functional impact of the excitatory and inhibitory contralateral pathways on the MGB and auditory processing. Acoustic stimuli were presented using pure tone pips and frequency modulated sweeps to assess the spectral and temporal responsiveness of neurons recorded in the MGB contralateral to the stimulus presentation, before and after optogenetic inhibition of the contralateral tectothalamic inputs. From our studies, we find that both the spontaneous and sound evoked activity in the MGB is altered significantly following optogenetic inhibition of these

tectothalamic pathways. The magnitude and directionality of these changes varied depending on the degree and nature of the optogenetic and acoustic stimulations. These studies corroborate our prior studies indicating a substantial neuroanatomical convergence of ipsilateral and contralateral tectothalamic inputs onto single MGB neurons. Together, these findings demonstrate a significant functional role for the contralateral tectothalamic inputs, one which may underlie the computations necessary for higher-order sound source identification and localization

Disclosures: J.A. Kara: None. **T. Vaughn:** None. **C.C. Lee:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.14/X22

Topic: E.05. Auditory and Vestibular Systems

Support: b

Title: Developing a Reliable Translational Startle-Based Biomarker

Authors: *Z. ENAYATI[1], S. YALCINOGLU[2], R. D. BRAUN[2], A. HOLT[2];
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Abstract: Noisy environments contribute to hearing loss and tinnitus, a prevalent phantom auditory percept. Despite its clinical impact, objective biomarkers for diagnosis and monitoring remain limited, and current assessment relies largely on subjective measures including questionnaires and psychoacoustic matching procedures. This limits reliability and disease progression tracking, highlighting the need for objective, reliable, and clinically scalable tools to diagnose the condition. We evaluated gap inhibition of the acoustic startle reflex (giASR) features in normal-hearing humans and in noise-exposed and control rats to identify translational giASR to support future reliability validation and potential sensitivity to tinnitus in humans.We used a repeated-measures giASR paradigm in 20 normal-hearing adults (20-65 years) and 9 male Sprague-Dawley rats. Human participants underwent audiometry confirming normal hearing and had no history of neurological or psychiatric disorders. Rats were assigned to noise-exposed and non-noise-exposed conditions and tested longitudinally over 12 weeks. Eyeblink EMG responses were recorded during sound-off startle (SOS), no-gap (NG), and gap-in-noise (G) conditions using broadband startle stimuli with background tones.Gap-induced inhibition of startle was robust in both humans and animals ($p < 0.05$), and background tones reduced startle magnitude. Human participants showed significant habituation across trials ($p = 0.014$). In rats, giASR features differentiated noise-exposed from non-noise-exposed groups: non-exposed animals showed sustained habituation over 90 days, whereas noise-exposed animals failed to exhibit normal habituation ($p < 0.05$).Shared giASR features, including startle magnitude suppression and habituation, were identified in both humans and rats, supporting the translational potential of these measures across species. The altered habituation observed following noise exposure further

suggests sensitivity to auditory dysfunction relevant to tinnitus. Future work will evaluate additional parameters, including sensitization, to identify the most reliable cross-species giASR phenotypes. These findings provide a foundation for linking mechanistic studies in animal models with objective biomarker development for tinnitus in humans.

Disclosures: Z. Enayati: None. **S. Yalcinoglu:** None. **R.D. Braun:** None. **A. Holt:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.15/X23

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant GM138023
NSF Cooperative Agreement No. OIA-2242771

Title: ZnT3 deletion from GABAergic neurons - consequences for context dependent auditory processing in mice.

Authors: E. TRATE[1], *C. T. ANDERSON[2];
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Abstract: Stimulus-specific adaptation is a prevalent sensory phenomenon in which repeated presentations of the same stimulus result in increasingly smaller neuronal responses to that stimulus, but neuronal responses to a different stimulus are maintained. The primary auditory cortex is crucial for these processes and is enriched with synaptic zinc, which plays an important role in modulating neuronal function and sound processing. Synaptic zinc within the brain is dependent on the zinc transporter protein ZnT3, which is responsible for loading zinc into vesicles to be released into the synapse. The ZnT3 transporter is expressed in both inhibitory and excitatory neurons in the auditory cortex, suggesting multiple effects of synaptic zinc release on inhibition and excitation during auditory processing. Previous work has shown the importance of inhibitory neuronal networks during stimulus-specific adaptation, while other studies have shown the effect of synaptic zinc on deviance detection and auditory behavioral processing. Here, we describe a newly created conditional mouse line in which ZnT3 is conditionally deleted from GABAergic somatostatin (SOM) neurons. We use this mouse to assess the interplay between ZnT3-dependent zinc and SOM neuron function during stimulus-specific adaptation and deviance detection using in vivo calcium imaging and mouse behavioral approaches. We perform stereotaxic injection of multiple AAV vectors to induce the expression of opsins and calcium sensors in specific cortical neuron types. We then perform wide-field calcium imaging of neuronal responses in awake, head-fixed mice during different sound paradigms to quantify the various aspects of stimulus specific adaptation. We find that ZnT3-dependent zinc in SOM neurons supports stimulus-specific adaptation and deviance detection in the auditory cortex. Understanding the roles of zinc from specific cortical cell types during context-dependent

sensory processing addresses a crucial gap in our knowledge about the synaptic and circuit mechanisms that support dynamic auditory processing across a range of ethologically relevant timescales.

Disclosures: E. Trate: None. **C.T. Anderson:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.16/X24

Topic: E.05. Auditory and Vestibular Systems

Support: NSF CAREER Grant IOS 2144831
St. Olaf Collaborative Undergraduate Research and Inquiry (CURI) Program
St. Olaf TRIO McNair Program

Title: Reproductive state shapes auditory perception and host-seeking behavior in Ormia ochracea

Authors: *L. J. BITNER[1], N. LEE[1,2];
[1]Biol., St. Olaf Col., Northfield, MN; [2]Biol. Sci., Univ. of Toronto Scarborough, Toronto, ON, Canada

Abstract: Internal physiological states can alter how animals perceive and respond to sensory information. Reproduction is a major life-history transition that can reshape neural processing and behavior, yet its effects on sensory systems remain poorly understood in insects. The acoustic parasitoid fly *Ormia ochracea* relies on hearing to locate singing crickets that serve as hosts for its developing larvae. We tested whether auditory sensitivity and host-seeking behavior change across reproductive states. Using free-walking and tethered-walking phonotaxis experiments and neurophysiological recordings, we compared unmated, mated, and gravid female flies carrying developed larvae. We discovered that gravid flies had lower behavioral response thresholds compared to unmated and mated female flies. Neurophysiological recordings revealed lower auditory thresholds in mated and gravid flies than in unmated female flies, particularly at frequencies corresponding to host cricket songs. These results show that reproductive state modulates auditory sensitivity and behavior in *O. ochracea*, likely enhancing host detection when female flies are carrying developing larvae. This heightened sensitivity may facilitate efficient localization of host crickets during the reproductive stage.

Disclosures: L.J. Bitner: None. **N. Lee:** None.

Poster

PSTR096: Temporal, Spectral, and Frequency Processing in Central Auditory Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR096.17/X25

Topic: E.05. Auditory and Vestibular Systems

Support: NSF Grant (IOS 2144831)

Title: Multidimensional encoding of temporal features underlies song recognition in the acoustic parasitoid fly Ormia ochracea

Authors: *M. PUGH;
St. Olaf Col., Northfield, MN

Abstract: Acoustic communication signals often contain complex temporal structure, yet the features that underlie signal recognition remain poorly understood, particularly in eavesdropping unintended receivers. The acoustic parasitoid fly Ormia ochracea is an eavesdropper that localizes host crickets by homing in on their calling songs. In Florida, the preferred host cricket produces calling songs characterized by stereotypic sound pulses repeated at 50 pulses per second and Floridan flies prefer this pulse rate. However, it is unclear whether this preference reflects sensitivity to pulse rate itself, or to the underlying temporal features that generate it. In this study, we independently varied pulse duration and interpulse interval across a broad stimulus space and quantified tethered walking phonotaxis on a spherical treadmill system using a switch-following paradigm. Behavioral results formed a structured tuning surface, with high performance values along a diagonal corresponding to 50 pps, as well as an extended region of elevated responses across a restricted range of pulse durations spanning a large range of interpulse intervals. However, responses failed to collapse across stimuli sharing the same pulse rate (or pulse period), which suggests that these features alone do not determine song recognition. Instead, behavioral tuning was best explained by the combined interacting effects of pulse duration and interpulse interval. These results demonstrate that song temporal pattern recognition in Ormia ochracea is multidimensional and cannot be reduced to a single parameter. We propose that apparent pulse rate tuning emerges as a projection of an underlying feature space rather than an explicitly encoded attribute. In addition, neurophysiological recordings from ascending auditory neurons suggest limited temporal pattern filtering in the thoracic ganglion, indicating that further processing likely occurs in the brain. Our findings highlight the importance of multidimensional representation in sensory processing and suggest that similar principles may govern signal recognition in both intended receivers and eavesdroppers.

Disclosures: M. Pugh: None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.01/X26

Topic: E.06. Vision

Support: Welcome Trust Investigator Award 210684/Z/18/Z

Title: An innate behavioural response to coarse visual patterns in mice reliant on melanopsin

Authors: *R. J. LUCAS, R. STORCHI;
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Abstract: Photoreception in the mammalian retina extends beyond rods and cones to a small number of melanopsin-expressing retinal ganglion cells (mRGCs). Melanopsin phototransduction applies a low pass spatiotemporal frequency filter to the visual scene and plays a critical role in behavioural and physiological responses to ambient light. Here we ask whether melanopsin also supports ethologically relevant responses to spatial patterns. Reasoning that the difference in brightness between ground and sky is the most ubiquitous low frequency pattern, we applied the environmental light field (ELF) method to describe vertical light gradients in an array of natural scenes at mouse-eye level. These revealed the expected vertical gradient, but strong scene-to-scene variation at moderately positive elevations. To determine whether mice use this signal to judge environment quality we modified the light:dark box forced choice paradigm to produce chambers with divergent vertical gradients. Mice preferred naturalistic gradients over featureless illumination and especially environments dim around the horizon. Recording of neural spike firing in the visual thalamus of mice freely exploring an environment with such a vertical gradient confirmed that this pattern was reflected in modulations in neural activity over frequencies (<1Hz) to which melanopsin is active. Behavioural preference for such vertical gradients was retained in mice lacking cone phototransduction (*Cnga3*$^{-/-}$), lost in melanopsin knockouts (*Opn4*$^{-/-}$), and matched the wavelength sensitivity of melanopsin in visually intact animals. Our data describe an innate preference for low spatial frequency patterns in mice and attribute an ethologically relevant behaviour to melanopsin photoreception.

Disclosures: R.J. Lucas: None. **R. Storchi:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.02/X27

Topic: E.06. Vision

Support: Templeton World Charity Foundation 0567
University of California Irvine Startup Fund
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Boston University UROP

Title: Figure-ground decoding in visual cortex tracks behavioral performance over and above physical stimulus strength

Authors: ***J. WANG**[1], E. OLSSON[2], M. L. EPSTEIN[3], K. TIAN[1], B. MANISCALCO[2], J. MOTZER[1], D. GAMBOA[1], M. NGUYEN[2], O. GRAHAM CASTANEDA[2], A. SHEN[2], M. SRIRAM[2], M. A. PETERS[2], R. N. DENISON[1];
[1]Psychological & Brain Sci., Boston Univ., Boston, MA; [2]Cognitive Sci., Univ. of California, Irvine, Irvine, CA; [3]Ctr. for Brain Imaging, New York Univ., New York, NY

Abstract: [Introduction] Figure-ground processing is a critical early step of object and scene perception. Although figure-ground signals have been observed in early visual cortex, it remains unclear the degree to which these signals reflect physical stimulus strength versus behavioral performance. [Methods] Thirty participants across two independent sites completed an fMRI figure-ground task over multiple sessions. Participants viewed brief (250 ms) texture-defined figure-ground stimuli with parametrically manipulated figure strength spanning five individually calibrated line length levels. On each trial, display quadrants contained either a figure-present stimulus, in which a vertical or horizontal oval figure was defined by a texture orientation that was orthogonal to the background (+/-45 degrees), or a matched figure-absent stimulus. For a post-cued quadrant, participants reported the oval's vertical or horizontal orientation, allowing us to calculate orientation discrimination accuracy on figure-present trials. We quantified figure-ground information in figure-responsive voxels in V1 - V3, which were identified in independent mapping runs. For each task run, we estimated condition-specific voxelwise responses using a GLM and used leave-one-run-out linear classification to decode figure presence from multivoxel response patterns. We used linear mixed models to relate decoding accuracy to the predictors of physical line length and performance accuracy, both individually and in combination. [Results] Decoding accuracy increased with line length level and could be predicted by either physical line length or behavioral performance accuracy, which were partially correlated. Model comparison indicated that behavioral performance better predicted decoding accuracy. Likewise, including both behavioral performance and physical line length improved model fit compared to physical line length alone, indicating that behavioral performance captured unique variance in decoding accuracy. [Conclusion] Multivariate visual cortical representations of texture-defined figures track behavioral performance for discriminating figure shape better than they track the physical stimulus strength, suggesting that figure-ground information in early visual cortex carries functional information over and above physical stimulus properties.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.03/X28

Topic: E.06. Vision

Support: Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB1010202)
National Natural Science Foundation of China (Grant No. W2432019)

Title: Closed-loop training aligns sensory subspace and perceptual decision in macaque V4

Authors: *J. HU[1,2], G. OKAZAWA[3,2];
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Abstract: Sensory cortices carry rich information about the physical world, but this information is useful only if downstream circuits read it out appropriately. An animal's ability to read out sensory signals is fundamental to perception, yet studying its mechanisms is challenging. Many studies have examined correlations between sensory neural responses and perceptual judgments, but the interpretation of such correlations remains controversial due to numerous intervening variables, such as the activity of unrecorded neurons. Furthermore, studies have often found that animals' choices do not align with the optimal decoding axis of sensory signals in sensory cortices, raising the question of whether there are constraints in the readout mechanism. Here, we introduce a novel neurofeedback (closed-loop) paradigm that allows us to directly prompt subjects to adjust the relationship between sensory neural activity and choice. The key idea is to train subjects to report specific patterns of population activity in a sensory area recorded online, regardless of the actual stimuli presented. To demonstrate this concept, we trained macaque monkeys on a visual change-detection task using shape stimuli, implanted an electrode array in visual area V4, and tested whether they could be further trained to detect fluctuations in V4 activity along a specific axis in neural state space. We selected optimal decoding axes for several visual features as a target for this closed-loop training. Strikingly, we found that the monkeys could increase the neuron-choice correlation along these axes. No changes in stimulus selectivity or noise correlations within the recorded population were found, suggesting that the behavioral changes were not driven by modulation of sensory neural activity itself. To further identify the mechanism, we built a feedforward model containing a pool of correlated sensory neurons with flexible readout weights. Changing the readout weights could quantitatively replicate the changes in neuron-choice correlation observed in the closed-loop condition, whereas altering other parameters, such as the correlation patterns of the sensory neurons, could not account for monkey experimental results. An additional control experiment revealed that the neuron-choice correlation did not change when the monkeys were rewarded randomly, regardless of V4 activity, under the same task setting. Together, our novel paradigm has revealed that sensory readout can be flexibly controlled and the alignment between stimulus and choice encoding can be improved beyond the level obtained by typical perceptual training.

Disclosures: J. Hu: None. **G. Okazawa:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.04/X29

Topic: E.06. Vision

Support: Intramural Research Program Grant ZIAMH002964
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Title: M4-ipRGCs regulate contrast sensitivity in vision

Authors: *K. DALY[1], X. LI[2], S. RATHORE[1], R. KOMAL[1], C. BEIER[1], G. P. OSTERMEYER[3], J. LEFFLER[4], N. M. ALAM[5], G. T. PRUSKY[5], P. ROBINSON[6], B. SIVYER[4], W. N. GRIMES[2], J. S. DIAMOND[2], R. L. BROWN[3], S. HATTAR[1];
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Abstract: Background: Light detected by photoreceptors is transduced and integrated by retinal ganglion cells (RGCs), which relay visual information to the brain. Approximately 5% of RGCs are intrinsically photosensitive (ipRGCs), directly detecting blue light via melanopsin and signaling independently of rod/cone input. ipRGCs mediate multiple non-image-forming functions including circadian photoentrainment, mood, cognition, sleep, feeding, body temperature, and pupil constriction. In mice, ipRGCs comprise six subtypes (M1-M6). While M1 ipRGCs are well characterized, directly linking other subtypes to behavior remains challenging.
Aims: We developed viral tools to label RGC subtypes and transiently manipulate their activity during behavior. Using intersectional genetics for in vivo manipulation of M4 ipRGCs (ONs alpha RGCs), we tested whether M4s primarily mediate image-forming vision rather than non-image-forming functions and sought to define their central targets and roles.
Methods: We identified parvalbumin as a candidate biomarker for selective M4 labeling using a two gene intersectional strategy. Intravitreal injection of a CRE-ON;FLP-ON INTRSECT reporter virus into *Opn4Cre;Pvalb-T2A-FlpO-D* mice labeled M4 axonal projections in a dual-recombinase-dependent manner. Intersectional chemogenetic viruses enabled selective activation or silencing of this subtype to probe function during in vivo behavioral assays.
Results: Viral tracing showed that M4 ipRGCs are absent from the hypothalamus, including the suprachiasmatic nucleus, but strongly innervate brain regions involved in image processing. We identified previously unknown projections to the nucleus of the optic tract, a component of the accessory optic system involved in horizontal gaze stabilization. Chemogenetic manipulation of M4s did not affect pupil constriction or circadian phase shifting. However, inhibition reduced contrast sensitivity during in vivo optomotor assays and cell-attached recordings, consistent with phenotypes observed in melanopsin-null mice, indicating a role in low-contrast (<10%) visual tracking. Conversely, activation increased contrast sensitivity in both behavioral and electrophysiological assays. Perforated-patch recordings suggest this effect arises from depolarization of resting membrane potential, increasing M4 ipRGC excitability.
Conclusion: This work establishes a strategy for selective manipulation of sparse RGC subtypes in vivo and identifies M4 ipRGCs as key mediators of melanopsin-dependent contrast sensitivity. Together, these findings demonstrate a prominent role for M4 ipRGCs in image-forming vision.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.05/X30

Topic: E.06. Vision

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Research to Prevent Blindness

Title: Latent representations of spatial information in V4 population activity during saccades

Authors: *G. WENG[1], H. AHN[1], B. NOUDOOST[2], N. NATEGH[1,2];
[1]Electrical and Computer Engin., [2]Ophthalmology and Visual Sci., Univ. of Utah, Salt Lake City, UT

Abstract: The brain transforms visual stimuli projected onto the retina into spatial representations of the external environment, yet the neural mechanisms underlying these representations remain poorly understood. Neurons in higher-order visual areas dynamically adjust their responses according to interactions between external factors, such as visual input, and internal factors, such as behavioral goals. Understanding how spatial information is encoded therefore requires examining neural activity as it changes alongside changes in visuospatial perception and behavior, such as during saccadic eye movements (saccades). A major challenge in characterizing these representations is the high-dimensional nature of neural activity, which arises from the interaction of multiple sensory, motor, and cognitive variables as well as the complex spatiotemporal structure of population dynamics. As modern recording technologies enable simultaneous measurements from increasingly large neuronal populations, there is a growing need for computational models that capture population dynamics while providing interpretable descriptions of sensory representations. To address this challenge, we develop a latent variable identification framework that captures low-dimensional representations of population spatiotemporal response dynamics during behavior. We apply this approach to electrophysiological recordings from V4 neurons obtained with long Neuropixels probes designed for nonhuman primates, which provide high-density recordings from large neuronal populations. During recordings, monkeys performed a visually guided saccade task while eye movements were monitored using a high-resolution eye-tracking system. These data enabled us

to quantify spatial information represented collectively by local neural populations around the time of saccades. Our results demonstrate that encoding models incorporating low-dimensional latent representations provide an interpretable description of neural population activity by identifying behaviorally relevant components embedded within high-dimensional activity patterns. This framework offers a foundation for future applications across diverse behavioral paradigms and brain regions, advancing our understanding of the population-level mechanisms that support visuospatial perception.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.06/X31

Topic: E.06. Vision

Title: Functional visual deficits associated with altered retinofugal connectivity in Olfactomedin 2 deficient mice

Authors: *K. LOFTIS[1,2], J. NIE[3], N. NAKAYA[2], S. I. TOMAREV[4];
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Abstract: Olfactomedin 2 (Olfm2) is highly expressed in the retinal ganglion cells (RGCs) during development and has been implicated in visual system function. However, the consequences of Olfm2 deficiency on visual physiology and behavior remain incompletely understood. To determine how loss of Olfm2 affects visual function, we performed flash electroretinography (fERG), pattern electroretinography (PERG), longitudinal optomotor response (OMR) testing, looming avoidance, and visual cliff assays in *Olfm2* knockout (KO) and wild-type (WT) mice. Retinal function assessed by fERG was preserved in *Olfm2* KO mice, with no significant differences in amplitudes or peak latencies compared with WT controls, suggesting that outer retinal function remains intact. In contrast, PERG recordings revealed significant reductions in P1 and N2-P1 amplitudes ($p < 0.01$ and $p < 0.05$, respectively), consistent with impaired RGC function and altered visual pathway signaling. Longitudinal OMR testing demonstrated a persistent reduction in spatial acuity beginning at postnatal week (PW) 7 and extending through PW26 (KO $\mu = 0.39$ cycles per degree [cpd], WT $\mu = 0.48$ cpd; $p = 0.00032$), while contrast sensitivity remained largely unaffected. These findings suggest a selective impairment in high-acuity visual processing. In contrast, looming avoidance and visual cliff performance (tested at PW7) were not significantly affected, indicating that those visually guided behaviors are preserved despite measurable physiological deficits and that Olfm2 deficiency differentially impacts distinct aspects of visual function. Functional deficits occurred in the context of reduced retinofugal projection strength observed in young adult *Olfm2* KO mice. Together, these findings suggest that abnormalities in retinal output pathways are

associated with selective impairments in visual processing. Further studies will be required to determine the mechanisms underlying the differential sensitivity of physiological and behavioral measures.

Disclosures: K. Loftis: None. **J. Nie:** None. **N. Nakaya:** None. **S.I. Tomarev:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.07/X32

Topic: E.06. Vision

Support: ZIAMH002966

Title: Task engagement modulates BOLD responses in early visual cortex

Authors: *P. KREYENMEIER[1], C. M. ZIEMBA[2], T. MORGAN[3], H. NIENBORG[4], E. P. MERRIAM[5];
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Abstract: Neurons in early visual cortex (EVC) are selective for low-level visual features and provide the building blocks of visual perception. Recent neuroimaging studies in monkeys and humans have shown that EVC exhibits intrinsic hemodynamic responses that are related to the task structure in the absence of visual stimulation. However, the origin and function of these task-related responses are poorly understood. Here, we test the hypothesis that task-related activity reflects changes in internal brain states, such as task engagement and overall arousal. We recorded behavioral performance, high-resolution eye tracking, and ultra high-field functional magnetic resonance imaging (7T fMRI) while participants (n=6) alternated between periods of engagement in a demanding visual task and periods of rest (with eyes open and under controlled visual stimulation). In a series of follow-up experiments, we tested variants of the task to test the role of temporal predictability, the decision, and the motor response. We found that eye metrics (microsaccades, blinks, and pupil size) were modulated with the task: during task engagement, microsaccades and blinks were suppressed while pupil size increased, reflecting periodic fluctuations in arousal state. fMRI-BOLD responses in EVC showed a similar periodic modulation. EVC exhibited widespread increases in response amplitude during rest, when subjects were disengaged from the task and in a low arousal state. These task-related responses were widespread across early visual areas and persisted across different control experiments: 1) when subjects were not required to provide a manual response, 2) when the timing of the task was unpredictable, and 3) when accounting for task-related blinking. Our findings demonstrate

that task-related BOLD activity in early visual cortex reflects changes in brain state, independent of visual stimulation, predictive processes, blinking, and response modality.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Research to Prevent Blindness

Title: Supervised Autoencoder-Based Source Separation of Local Field Potentials Using Concurrent Spiking and Interareal Signals

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Abstract: Identifying the distinct sources underlying local field potentials (LFPs) in neuronal populations is essential for understanding the computations that emerge from complex intra- and interareal neural interactions. Blind source separation (BSS) approaches used for decomposing mixture signals face challenges when applied to neural signals due to the unknown and potentially nonlinear mixing of underlying sources, the unknown number of contributing sources, and the unknown dependency structure among local and distant LFPs as well as between LFPs and other ongoing neural activity such as spiking responses. Conventional unsupervised BSS methods typically focus on capturing dominant variance under assumptions of linear mixing, fixed source dimensionality, or predefined dependency structures, for signal decomposition, limiting their ability to capture computations arising from the integration of diverse neural activity and to identify behaviorally relevant neural dynamics. To address these limitations, we developed a supervised autoencoder-based source separation framework that jointly leverages simultaneously recorded LFP and spiking activity from prefrontal and visual cortical areas. Rather than relying on solely on mathematically defined assumptions for optimal reconstruction of the original mixed LFP signals, our framework incorporates biologically informed constraints derived from multi-regional and multimodal neural signals. Specifically, the model identifies a latent subspace whose dimensions represent decomposed neural sources by

minimizing reconstruction error of the original LFP signals in visual areas, while incorporating concurrent prefrontal activity and local spiking signals as regularization terms. We applied this framework to LFP and spiking data recorded from a single electrode in the frontal eye field (FEF) part of prefrontal cortex and a multielectrode array in area V4 while monkeys performed a visual localization task during saccadic eye movements. Our proposed autoencoder decomposition successfully isolated a distinct prefrontal-driven oscillatory component communicated with area V4 as well as oscillatory sources intrinsic to the V4 network. These components provided a latent oscillatory representation capable of predicting the saccade-induced changes perceived visual stimulus location reported by the monkeys. Together, these findings provide a general framework capable of identifying behaviorally relevant population dynamics applicable to various brain areas and tasks.

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Poster

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Title: Natural Scene Segmentation Dynamics and Bayesian Spatial Priors in Autism

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Abstract: Segmenting natural scenes into perceptual units such as objects and parts is central to sensory processing. Our recent Bayesian account proposes the brain does this by combining sensory evidence with prior expectations about the spatial structure of visual objects. Influential theories of autism spectrum disorder (ASD) hypothesize that the contribution of Bayesian priors is attenuated in ASD. This could explain previous findings of atypical segmentation in ASD, but a direct test in naturalistic vision has been limited by two main barriers. First, most studies of segmentation in ASD rely on simplified stimuli, such as arrays of dots or lines, that lack the statistical structure and semantic contents of real scenes. Second, few studies resolve the perceptual and cortical dynamics over which the influences of Bayesian priors on segmentation unfold, leaving open when, not just whether, priors shape perception in ASD. To address those shortcomings, we adopt a trial-based paradigm in which observers judge whether pairs of cued regions of a natural image belong to the same segment. These measurements provide trial-by-

trial reaction times to probe the perceptual dynamics of segmentation and, across trials, a per-participant estimate of the spatial Bayesian prior, i.e. the tendency to group neighboring regions regardless of image content. Here we apply this paradigm with concurrent EEG recording in neurotypical adults and IQ-matched adults with ASD. We characterize perceptual and cortical segmentation dynamics to test whether the spatial prior and its neural correlates are altered in ASD. At the group level, in ASD participants the reaction times are slower and the occipital event-related potentials are delayed and more spatially diffuse. Within each group, reaction times are modulated by congruence of single-trial judgments with each participant's spatial prior, though this modulation is weaker in our current ASD sample. We are now using multivariate decoding to test whether trial-by-trial cortical activity contains information about the relationship between observers' judgments and the spatial prior. Preliminary analyses suggest that this information may be expressed during a sustained post-stimulus window in the neurotypical cohort, motivating ongoing tests in the growing ASD sample. Together, these results demonstrate a reproducible pipeline linking perceptual and cortical dynamics and Bayesian priors, for studying segmentation of natural scenes in ASD.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Title: Increases in stimulus strength increase membrane potential variability in behaving macaque V1

Authors: *B. LI[1], E. SEIDEMANN[2], N. J. PRIEBE[3];
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Abstract: Increases in stimulus strength increase membrane potential variability in behaving macaque V1 Authors: Baowang Li[1-5], Eyal Seidemann[1, 3-5] and Nicholas J. Priebe[1-4] [1]Center for Perceptual Systems, The University of Texas at Austin [2]Center for Learning and Memory, The University of Texas at Austin [3]Center for Theoretical and Computational Neuroscience [4]Department of Neuroscience [5]Department of Psychology **Disclosures:** Baowang Li: None. Eyal Seidemann: None. Nicholas J. Priebe: None **Abstract** Neocortical responses are variable: repeated presentations of the same visual stimulus evoke distinct patterns of activity in V1 neurons. This variability is not just noise—it influences perceptual decisions and reflects mechanisms that control neuronal gain and selectivity as afferent drive changes. A striking

example is contrast-invariant orientation tuning in V1, where neurons maintain tuning width despite large changes in stimulus contrast. Previous work suggests that this invariance depends on contrast-dependent reductions in membrane potential (Vm) variability, which modulate spiking gain. However, these observations come primarily from anesthetized preparations, where network dynamics differ substantially from the awake state. Here, we recorded intracellularly from V1 neurons in awake macaques performing a fixation task while viewing gratings of varying contrast and orientation. Contrary to the anesthetized results, we find that Vm variability increases with contrast—challenging existing models that link increases in afferent drive to Vm variance quenching. To examine the effect of contrast on orientation tuning and on the Fano factor, we made extracellular measurements of spiking activity using either laminar probes or neuropixels electrodes. We observed systematic changes in V1 neurons' orientation tuning with contrast, demonstrating a lack of contrast-invariant tuning in awake macaque V1. In addition, consistent with previous results, we observed a reduction in the Fano factor with increasing contrast, demonstrating decoupling between Vm and spiking variabilities. Overall, our results highlight the profound influence of cortical state on variability and tuning, and suggest that network models linking increases in afferent drive to Vm variance quenching should be revised.

Disclosures: B. Li: None. **E. Seidemann:** None. **N.J. Priebe:** None.

Poster

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Topic: E.06. Vision

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Title: Perceptual training generates laminar specific distortions of task cue neuronal representations in the mouse V1.

Authors: *V. C. PUYO, J. CORBO, H. KHDOUR, P.-O. POLACK;
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Abstract: Primary cortices have long been viewed as faithful encoders of the sensory world; yet accumulating evidence suggests that experience and training actively reshape their representations, refining the extraction of meaningful information to support improved behavioral performance.
We previously demonstrated in layer 2/3 (L2/3) of mouse primary visual cortex (V1) that orientation discrimination training induces a feature-space surround suppression: neurons tuned to orientations adjacent to the task cues are selectively suppressed, distorting the representation space and pulling population activity toward the representation of behaviorally relevant stimuli. However, the cortex is not a uniform structure, with each layer implementing distinct computational roles; this transformation could therefore be specific to L2/3 or reflect a broader

translaminar principle. Investigating the laminar distribution of feature-space surround suppression will help us understand its circuit origins and whether reshaped representations propagate through cortical layers to guide behavior.
Using two-photon calcium imaging, we characterized population responses across V1's L4 and L5 in mice performing a Go/NoGo orientation discrimination task. A clear laminar dissociation emerged: L5, like L2/3, exhibited a distortion of the orientation space, i.e., orientations flanking the task cues were represented as the task cues themselves, while L4 maintained a faithful representation of any presented stimulus orientation. This result suggests that feature-space surround suppression does not originate in layer 4 but emerges within the cortical circuits of layer 2/3, potentially through recurrent intracortical dynamics and/or top-down feedback.
Given L5's role as a major output layer with subcortical projections implicated in decision-making, we then asked whether L5 neurons encode signals beyond stimulus identity. Activity-based clustering reveals functional subpopulations including reward and outcome-selective neurons, confirming L5 not merely as a relay of L2/3 output, but as an active site where task-dependent sensory reshaping converges with behavioral signaling. Together, our results demonstrate a laminar gradient of representational transformation, from ground-truth sensory-driven representations to task- and behavior-related ones, revealing an unexpectedly active role for V1 in the sensory-to-decision transformation process.

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Poster

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Topic: E.06. Vision

Title: Intrinsic Neuronal Timescales in Visual CortexPredictthe Representation of Higher-Order Prediction Errors

Authors: *M. AZMI;
Vanderbilt Univ., Nashville, TN

Abstract: Intrinsic Neuronal Timescales in Visual Cortex May Underlie the Representation ofHigher-Order Prediction Errors Mazyar Azmi, Yihan S. Xiong, Hamed Nejat, Jacob A. Westerberg, André M. BastosPrediction error responses depend on the ability of cortical circuits to compare incoming sensoryinput with expectations formed over time. Because neurons differ in their intrinsic temporalintegration windows, we hypothesized that intrinsic timescale may help determine which neuronsparticipate in encoding higher-order visual surprises. To address this, we performed multi-area,high-density, laminar neurophysiology recordings across six visual cortical regions in mice (V1,LM, RL, AL, PM, AM; N = 5062 single-units) and twelve visual and higher-order cortical areasin macaques (V1, V2, V3, V3A, V3D, V4, MT, MST, TEO, FEF, PFC, PMD; N = 2147 single-units), from 15 mice and 2 macaque monkeys during passive

viewing of structured visualsequences designed to evoke global and local oddball responses. For each neuron, we quantifiedoddball encoding using effect-size measured that compared experimental and control spikeresponses after accounting for adaptation-related response changes within each sequence. Wethen asked whether oddball encoding could be predicted from intrinsic neuronal properties.Linear models were fit separately by species using visual hierarchy score, waveform duration,firing rate, intrinsic timescale, and timescale latency, and intrinsic complexity. These modelspredicted local and global oddball response magnitude above chance in held-out data. Predictionwas stronger for local oddball magnitude, especially in mouse, than for global oddballmagnitude. Intrinsic timescale provided a small but reliable prediction for global oddball in allmapped units, with a larger contribution in macaques, and within-area analyses suggested thatthis relationship was not merely due to area-level differences. These findings support a a modelin which intrinsic temporal dynamics are relevant to visual oddball encoding, but they are onecomponent of a broader set of physiological and circuit-level factors. Rather than determiningglobal prediction error encoding outright, intrinsic timescale may bias neurons toward greaterparticipation in temporally extended sensory inference.

Disclosures: M. Azmi: None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Title: Brainwide neural correlates of visual behavior in awake marmosets

Authors: *A. JASANOFF[1], **W. TU**[1], Y. JIANG[1], B. STALLINGS[1], Y. KE[1], Y. CHEN[2], G. FENG[2];
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Abstract: Visual perception is an active process: what an animal fixates or tracks with its eyes determines which information is sampled from the environment and propagated through the brain. Visual attention in turn is thought to be guided by competition between frontal and sensory brain regions, tempered by affective influences arising from limbic structures. To study how these processes interact at a brain-wide level, we performed functional magnetic resonance imaging (fMRI) and recorded ocular data from marmosets as they freely viewed videos or engaged in a binocular rivalry task. We compared behavior and neural activity measures among wild type monkeys and animals bearing a mutation in the *SHANK3* gene, which models an autism spectrum disorder associated with perturbed visual behavior and cognition. By comparing eye-tracking data with fMRI, we identified distributed neural correlates of stimulus fixation,

saccade frequency, and attentional switching in the rivalry task. Both sensory and frontal regions exhibited task dependence, with particular association of fixation-related variables to prefrontal areas. Mutant animals displayed behavioral hallmarks of reduced attention accompanied by neural activity differences consistent with joint involvement of top-down and bottom-up contributions. To obtain mechanistically deeper information about the interplay among neural components in visual behavior, we are applying a genetic reporter for fMRI that reveals activity in brain-wide inputs to virally targeted sites. We describe initial experiences with the reporter applied to visual structures in awake marmosets.

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Poster

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Title: Contributions of Ventral Visual Cortical Areas V4 and PIT to Binocular Disparity Processing

Authors: A. NARMASHIRI[1], J. E. SMITH[2], K. KRUG[4], ***A. J. PARKER**[3,1,5];
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Abstract: Early lesion evidence pointed to a role of posterior temporal cortex (area TEO) in processing stereoscopic disparity, also supported by single-unit recording studies. The transition of disparity processing from middle-level areas such as V4 into TEO is less clear. Here we made direct, simultaneous comparisons between V4 and TEO by recording neuronal population activity from V4 and TEO using pairs of Utah arrays in two macaque monkeys, performing a disparity detection task using random-dot stereograms (RDSs). Monkeys fixated a small spot while 4 RDS stimuli (center 6 degrees, annular surround 1 degree always at zero disparity), with a range of 13 possible baseline disparities in the center (between 0 and +/- 0.5 degrees) were displayed for 1s, after which an extra disparity (0, +/- 0.05, +/- 0.1 degrees) was added to the centre region of one of these stimuli. Animals indicated detection of this change by a saccade to the centre of this RDS. Behavioral performance was summarized with %correct and reaction time measures. We identified a total of 396 disparity-tuned units in V4 and 147 in TEO (Monkey

M135: 173 V4 and 85 TEO; Monkey M137: 223 V4 and 62 TEO), recorded over 4 days in each case. At the neuronal level, both V4 and TEO units exhibited selectivity for centre baseline disparity, but the population fraction of units showing disparity tuning was lower in TEO (45% and 15% in each animal) than V4 (65%). To evaluate the timing of disparity specific responses, we applied a sliding temporal window (10ms) for calculation of the disparity discrimination index. Disparity specific activation in V4 led activation in TEO by ~30ms. We investigated whether neural responses in the mid-level ventral visual pathway to popout disparity changes are organized relative to each unit's preferred disparity. Specifically, we compared neural activity when pop-out disparity moves towards versus away from this preferred baseline value. On correct trials, pop-out events shifting toward the preferred disparity evoked a pronounced increase in firing rate, whereas shifts away from the preferred disparity produced comparatively weaker responses. This effect was stronger in V4 than TEO. During incorrect trials both areas showed a marked reduction in this differential modulation. We conclude that disparity specific activation in both V4 and TEO reflects a combination of sensory preferences for the stimulus and decision-related activations.

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Poster

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Title: Artificial visual percepts: optogenetic vs electrical stimulation of primate visual cortex

Authors: *J. CADENA-VALENCIA[1], M. FALKOWSKA-KISIEL[1], K. LIZA[1], J. GREILSAMER[1], D. GHEZZI[3], M. C. SCHMID[2];
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Abstract: Visual cortical prostheses aim to restore vision by stimulating neurons in visual cortex to evoke artificial visual percepts (phosphenes). While electrical stimulation has long been used for this purpose, optogenetic approaches promise improved spatial resolution through greater cell-type specificity. However, despite widespread success in rodents, translating optogenetic stimulation to primate visual cortex has proven challenging, and it remains unclear whether optogenetic stimulation can reliably induce perceptual experiences in primates.
Here we directly compare electrical and optogenetic stimulation in two macaque monkeys trained to report phosphene perception using vision-guided eye movement tasks. We found that

both stimulation modalities evoke phosphenes of comparable spatial extent, approximately 1° of visual angle. However, phosphene brightness induced by optogenetic stimulation is consistently reduced relative to electrical stimulation and does not increase proportionally with stimulation strength. We further relate these findings to detection paradigms in which optogenetic stimulation appeared unable to evoke phosphenes.
Analysis of electrophysiological responses indicates that optogenetic stimulation is most effective when it engages population activity patterns that resemble natural visual activation of V1 circuits. When such activation patterns are weaker or diverge from visually evoked responses, perceptual reports are correspondingly reduced.
Together, these results provide evidence that optogenetic stimulation of primate visual cortex can evoke artificial visual percepts, while highlighting the importance of recruiting appropriate cortical population dynamics for effective visual prosthetic stimulation.

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Poster

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Title: Frequency-dependent after-effects of transcranial alternating current stimulation on visual cortical activity and contrast perception in macaques

Authors: N. CHAMANI, J. GREILSAMER, M. FALKOWSKA-KISIEL, K. LIZA, J. CADENA-VALENCIA, ***M. C. SCHMID**;
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Abstract: The neural mechanisms through which transcranial alternating current stimulation (tACS) influences cortical processing and perception remain incompletely understood, particularly the persistent effects that outlast stimulation. Here, we investigated whether frequency-specific tACS targeting a V1-extrastriate visual network modulates neural excitability and visual contrast perception in rhesus macaques (*Macaca mulatta*). Two animals performed a two-alternative forced-choice contrast-detection task while electrophysiological activity was recorded using multi-contact laminar probes in V1. Anti-phase tACS was delivered between V1 and an extrastriate electrode positioned approximately over areas V4/MT at either 10 Hz or 60 Hz, with active sham and no-stimulation control conditions. Neural activity and behaviour were assessed during 15-min periods before and after stimulation.
Behaviourally, both 10 Hz and 60 Hz tACS improved contrast-detection sensitivity relative to

control sessions (average d′ increase ~0.5). Electrophysiologically, 10 Hz stimulation induced a persistent enhancement of visually evoked responses in V1, approximately doubling firing-rate modulation relative to control sessions ($p = 0.0011$, $n = 60$ units), accompanied by increased baseline excitability. In contrast, 60 Hz stimulation produced weaker, non-significant effects on response gain ($p = 0.16$, $n = 47$ units). Preliminary depth-resolved analyses suggest stronger modulation in supragranular and infragranular layers following 10 Hz stimulation, whereas 60 Hz and control conditions showed no consistent laminar pattern.
These findings demonstrate persistent after-effects of tACS on visual cortical processing and perception in awake macaques. While behavioural improvements were observed following both stimulation frequencies, robust increases in V1 excitability and visually evoked response gain were specific to 10 Hz stimulation, indicating frequency-dependent effects on visual cortical circuits.

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Poster

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Title: Disentangling vision from space in mouse primary visual cortex

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Abstract: Neural responses in the mouse primary visual cortex (V1) are modulated by the position of the animal in its environment. This was previously demonstrated in a strictly repeating virtual corridor, by comparing neuronal responses at their peak location to those at another visually identical location (Saleem et al., 2018). While this experimental design provides evidence for the presence of modulation by spatial position, it cannot capture the full profile of spatial modulation across the corridor. Here, we developed a virtual reality framework designed to disentangle visual and spatial signals through cue repetitions and manipulations. Mice traversed a 200 cm long virtual corridor featuring four visual landmarks superimposed on a smoothly varying background texture. To decouple visual and spatial signals, visual cues were repeated according to two different out-of-phase patterns: vertical grating and plaid landmarks each appeared at two locations separated by 80 cm, while background textures repeated with a distinct 24-cm periodicity. Additionally, systematic perturbations were introduced in a subset of trials, where landmarks were either omitted or swapped in position, further breaking the correlation between vision and space. This design provided the statistical power to fit a GLM that identified the respective contributions of visual features, and spatial positions across the entire corridor (Morimoto et al., 2025). We applied this framework to layer 2/3 V1 population responses collected using two-photon calcium imaging in four mice, recording activity from 10,233 excitatory neurons expressing jGCaMP8m. By leveraging the variance in responses to omissions, swaps, and background repetitions, the GLM isolated significant spatial components in a large fraction of V1 neurons. The recovered spatial tuning profiles were heterogeneous, displaying single and multi-peaked spatial components across the 200 cm trajectory. These findings show that spatial signals in V1 are diverse and present throughout the environment. This framework also provides a general method to characterize the modulation of sensory responses by spatial signals in other cortices.

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Poster

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Title: Visual Responses in different spatial and global contexts in mouse primary visual cortex

Authors: *D. TONG[1], M. TAKIGAWA[2], E. A. HORROCKS[2], C. BARRY[3], A. B. SALEEM[2]; [1]Inst. of Behavioural Neurosci., Univ. Col. London, LONDON, United Kingdom; [2]Inst. of Behavioural Neuroscience, Exptl. Psychology, Univ. Col. London, London, United Kingdom; [3]Cell & Developmental Biol., UCL, London, United Kingdom

Abstract: While primary visual cortex (V1) has traditionally been viewed as a visual feature detector, recent work shows V1 can additionally be modulated by spatial position - responding differently to visually identical landmarks present in different spatial positions within a virtual reality room. Does such a modulation of responses extend to larger differences in context? For example, when the same image is presented in different virtual rooms, rather than just different positions in a room?

We investigated this using simultaneous Neuropixels recordings in V1 and medial entorhinal cortex (MEC) while mice (n = 5) navigated two virtual rooms. Crucially, both rooms contained the same visual landmark at two matching positions, creating a hierarchical design (2 positions in 2 rooms) that allowed us to disentangle the influence of spatial position and room identity.

If V1 acts as a visual feature detector, V1 neurons should show identical responses to all four shared identical landmarks across the two rooms. However, we found that only about half of tuned neurons responded in the same magnitude to all four identical landmarks regardless of the spatial position and room identity the animal was at. Instead, confirmed by a two-way ANOVA, the other half of the tuned neurons showed a degree of influence by spatial position and room identity exceeding the expected number of modulated neurons by chance. A large fraction of them were significantly modulated only by the room identity, while another independent fraction of them were influenced only by the same spatial position modulation in both rooms. There is also a group of neurons modulated by joint effects of both spatial position and room identity. We confirmed the results using a GLM approach to account for potential differences related to running speed changes. MEC neurons re-mapped to have distinct representations of the two rooms. To examine shared population dynamics, we applied Factor Analysis and evaluated latent geometries. V1 and MEC exhibited distinct latent architectures. V1 population trajectories anchored to local visual landmark identity but not MEC, showing significantly lower geometric distances between identical landmarks than other landmarks in the VR. Both V1 and MEC population geometries separated the shared identical landmarks based on the global environmental context, showing significantly larger across-track distances than within-track distances.

These findings demonstrate that V1 generates unique representations for identical visual inputs, resolving sensory ambiguity in both spatial position and global context.

Disclosures: D. Tong: None. **M. Takigawa:** None. **E.A. Horrocks:** None. **C. Barry:** None. **A.B. Saleem:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.19/Y11

Topic: E.06. Vision

Support: NIH Grant EY005253

Title: Temporal potentiation of human pupil constriction during near-distance viewing

Authors: *U. MAHARJAN, S. DELLOSTRITTO, M. MAHAT, J. JIN, M. W. DUL, J.-M. ALONSO;
SUNY Col. of Optometry, New York, NY

Abstract: Modern visual behaviors have shifted markedly toward sustained near-work activities that require prolonged lens accommodation. We have previously shown that repeated lens accommodation to -5 diopters causes a pronounced temporal potentiation of both pupil constriction and horizontal eye vergence (Maharjan et al., 2026). Here, we investigated whether such temporal potentiation is also induced by near-work activities at focus. We measured pupil size and horizontal eye vergence in two different visual conditions: monocular viewing with head-mounted visual displays, and binocular viewing in the open with free head movement. 18 adults and 47 children wore a head-mounted display with an eye tracker (HTC VIVE Pro Eye, maximum luminance: 110 cd/m^2), and signaled the location of a light or dark peripheral target. The adults signaled left-right location with a hand clicker (92 different locations within 5-30 degrees eccentricity, 5-90% Michelson contrast). The children made saccadic eye movements towards the target (4-92 different locations, 5-30 degrees eccentricity, 7 - 90% Michelson contrast). 16 adults wore eye-tracking glasses (Neon Pupil Labs) while reading binocularly an article for ten minutes on a computer monitor in a dark room (black text, white background, luminance 24.5 cd/m^2). Our results demonstrate that pupil size decreases with time under both monocular and binocular conditions (monocular: r mean/ median ± std: -0.58/-0.71 ± 0.32, p: 3.27 x 10^{-4} for adults, and -0.34/ -0.40 ± 0.29, p: 8.58 x 10^{-8} for children; binocular: r mean/ median ± std: -0.41/ -0.57 ± 0.49, p: 0.0097 for right eye, and -0.43/ -0.51 ± 0.49, p: 0.0097 for left eye, Wilcoxon sign-rank tests). The pupil decrease was small but very consistent (linear slope within 5-10 minutes, mean/median ± std: -60/ -50 ± 40 microns/min, p: 1.8 x 10^{-4} for monocular viewing in adults, -70/ -60 ± 100 microns/min, p: 1.2 x 10^{-7} for monocular viewing in children, -20/ -30 ± 30 microns/min, p: 0.02 for binocular viewing in adults). Unlike pupil size, horizontal eye vergence decreased over time in children (monocular: r mean/ median ± std: -0.26/ -0.33 ± 0.31, p: 1.18 x 10^{-5}, Wilcoxon sign-rank test), but not in adults (monocular: r mean/median ± std: -0.18/-0.25 ± 0.47, p: 0.122, binocular: 0.21/ 0.51 ± 0.68, p: 0.18, Wilcoxon sign-rank tests). Taken together, these results demonstrate that near-work activities are associated with a temporal potentiation of pupil constriction not coupled to an increase in horizontal eye vergence. The increase in pupil constriction that we demonstrate could compromise retinal illumination when doing near-work activities at low light and increase the risk of developing myopia.

Disclosures: U. Maharjan: None. **S. Dellostritto:** None. **M. Mahat:** None. **J. Jin:** None. **M.W. Dul:** None. **J. Alonso:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR097.20/Y12

Topic: E.06. Vision

Support: NIH Grant EY005253
BSK Fellowship 2024

Title: Pronounced deficits of peripheral and upper-field vision in human myopia

Authors: *S. DELLOSTRITTO[1], M. W. DUL[1], J. JIN[1], H. RAHIMI NASRABADI[2], N. PATEL[3], J.-M. ALONSO[1];
[1]SUNY Col. of Optometry, New York, NY; [2]Rockefeller Univ., New York, NY; [3]Univ. of Houston, Houston, TX

Abstract: Myopia (nearsightedness) is a highly prevalent visual disorder with increasing incidence and unclear etiology. Prior work suggests ON-OFF pathway imbalances contribute to myopia susceptibility, and we previously demonstrated functional ON pathway deficits in adult myopia. Here, we further characterize ON pathway dysfunction in adult and adolescent myopia using psychophysical ON-OFF perimetric testing. Eighteen adults (25.8±2.8 years) and 39 children (13.3±1.7 years) with emmetropia or myopia (defined by refractive error; adults: plano to −9.50 D; children: +0.38 to −6.50 D) completed peripheral detection tasks using light and dark targets in a head-mounted display (HTC Vive Pro Eye; max luminance 110 cd/m²). Performance was quantified as percent incorrect responses. Wide-field Spectralis OCT measured retinal ganglion cell layer (RGCL) thickness, and axial length (AL) was obtained using Lenstar LS-900 or Heidelberg Anterion. In adults, increasing myopia was associated with greater detection errors that increased with eccentricity ($p=0.03$, $r=0.971$) and were larger in the upper visual field ($p=0.004$, $r=0.996$). Light-dark error differences in the upper field increased with eccentricity ($p=0.031$, $r=0.912$) and correlated with AL at 25° ($p=0.036$, $r=0.498$). Thinner RGCL was associated with greater detection errors across eccentricities ($p<0.001$). RGCL thickness was greater in the superior retina (lower visual field), and the upper-lower asymmetry decreased with eccentricity ($p=0.032$, $r=-0.910$), but was not related to AL. In children, RGCL thickness was negatively correlated with detection errors at 5°, 10°, and 25° (all $p<0.05$), strongest at 5° ($p=0.0009$, $r=-0.72$). Children exhibited larger saccadic amplitudes (12.6°±1.8 vs 13.8°±1.4; $p=0.0001$) and dysmetria (0.12°±0.13 vs −0.05°±0.13; $p=0.0006$) in the lower versus upper field indicating additional functional asymmetries. In a subset of participants (children n=26; additional adults n=5) who completed a secondary contrast sensitivity task at 15° showed poorer performance in children at low contrast (control: $p=0.03$; myopia: $p=0.002$), with myopic children showing greater errors than emmetropic children ($p=0.03$). Together, these findings demonstrate pronounced spatially asymmetric deficits in myopia that increase with eccentricity and axial length and are not fully explained by excessive retinal stretching associated with progressive myopia.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

Location: WCC Halls A-C

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Program #/Poster #: PSTR097.21/Y13

Topic: E.06. Vision

Support: NIH Grant R01EY03450

Title: Spike generation sharpens the spatial and temporal organization of receptive fields in visual cortex of the awake rabbit

Authors: *N. L. RAFFONE[1,2], M. CHISTYAKOVA[1], J.-M. ALONSO[3], M. A. VOLGUSHEV[1,2], Y. I. BERESHPOLOVA[1,2];
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Abstract: Understanding how visual cortical neurons transform synaptic input into spike output is fundamental to understanding visual processing and perception. Traditionally, cortical receptive fields (RF) have been studied using extracellular recordings, which assess spike output of neurons. Previous intracellular studies have demonstrated that stimulus selectivity is enhanced upon transformation of postsynaptic potential (PSP) into spike responses; however, experiments were performed in anesthetized, immobilized animals, under conditions known to alter cortical state, network activity, and sensory responses. It remains unclear how the transformation of synaptic input into spike output shapes RF structure in the normally functioning awake visual cortex. To address this question, we made intracellular recordings from neurons in V1 of awake, head-fixed rabbits and mapped RFs using sparse noise stimuli. RFs were calculated separately from PSP (PSP-RF) and AP (AP-RF) responses, allowing direct comparison of synaptic input and spike output in individual cells. We find that ON and OFF subfields of AP-RFs have significantly smaller area than those of PSP-RFs (ON: subfields, 18.0 $\pm$ 3.2 vs 29.2 $\pm$ 3.4 deg^2, $p < 0.001$, N=17; OFF: 14.8 $\pm$ 2.1 vs 25.4 $\pm$ 3.1deg^2, $p < 0.001$, N=20) and had less overlap (32 $\pm$ 6 vs 49 $\pm$ 5%, $p < 0.05$, N = 15) indicating that spatial precision of RFs is increased upon PSP-to-spike transformation. Separation of the centers of ON and OFF subfields and their elongation were unchanged. In several cells, PSP-RFs revealed convergent ON and OFF synaptic inputs, yet responses to one stimulus polarity remained subthreshold and no AP-subfield was detected. Extracellular recordings would erroneously classify such cells as only-ON or only-OFF and underestimate the diversity of synaptic inputs received by cortical neurons. AP-RFs exhibited significantly faster temporal dynamics than PSP-RFs. AP-RFs appeared only few milliseconds after PSP-RFs and had approximately 50% shorter durations of both ON and OFF subfields (ON: cells, 17.0 $\pm$ 1.3 vs 32.8 $\pm$ 3.0 ms, $p < 0.001$, N = 17; OFF: 16.2 $\pm$ 1.2 vs 32.0 $\pm$ 3.5 ms, $p < 0.001$, N = 20). To conclude, upon transformation of synaptic input into spike output both the area of RFs and duration of their spatio-temporal profile decrease. Together, these results demonstrate that the spike generation mechanism acts as a powerful filter that sharpens both the spatial and temporal organization of visual receptive fields in the awake cortex.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Topic: E.06. Vision

Support: NEI Grant R01EY021833
NEI Grant R01-EY08890

Title: Priming of attentional selection reshapes V4 selection drive without altering oscillatory dynamics

Authors: *S. LI[1], T. J. PALMERI[1], G. LOGAN[1], J. D. SCHALL[2], J. A. WESTERBERG[3,1]; [1]Vanderbilt Univ., Nashville, TN; [2]Biol., York Univ., Toronto, ON, Canada; [3]Dept. of Vision and Cognition, NIN-KNAW, Amsterdam, Netherlands

Abstract: Sensory neural responses in cognitive tasks are multiplexed, combining intrinsic circuit dynamics with behaviorally relevant signals. In macaque V4, for instance, spiking responses to visual search targets gradually diverge from responses to surrounding distractors. This divergence unfolds on top of prominent stimulus-evoked oscillations. Priming of popout, in which the target color repeats across trials, accelerates this divergence. However, because oscillatory dynamics also shape apparent discrimination timing, it remains unclear whether priming alters the oscillatory dynamics or the timing of target-distractor discrimination. We fit a cascade model to laminar V4 multiunit activity from two adult male macaques (n=29 sessions) performing a color singleton visual search task, decomposing recorded V4 responses into a shared oscillatory component and separate target and distractor selection signals. The model recovered an oscillatory frequency of 20.5 Hz, converging with prior spectral evidence for beta-band oscillations in V4. Oscillatory frequency and response onset latency were both higher in superficial than deep layers (Δ=2.06 Hz, p=0.005; Δ=3.1 ms, p=0.025; Wilcoxon signed-rank). Across n=13 sessions, oscillatory frequency and decay rate were both unchanged from weak (trials 1-3) to strong (trials 4-8) priming (p=0.455; p=0.787), despite robust reaction time facilitation (−11 ms, p<0.001). Priming instead selectively altered the selection signals: the target signal accumulated faster (by 24.9 ms, p=0.0009) while an early stimulus-driven response was reduced (p=0.034; n=14 sessions). These findings suggest that priming of popout accelerates V4 target selection by acting on driving inputs while preserving oscillatory dynamics.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Program #/Poster #: PSTR097.23/Y15

Topic: E.06. Vision

Support: EIC Grant 101071015
Fyssen Foundation

Title: Neuronal activations induced by monopolar and bipolar microstimulation in V1 and V2

Authors: *O. M. WALLIS[1,3], M.-A. LAURENT[3,1], M. SCHELLES[2,4], F. CEYSSENS[4], P. JANSSEN[1,3];
[2]Electrical Engin., [1]KU Leuven, Leuven, Belgium; [3]Lab. for Neuro- and Psychophysiology, KU Leuven, Leuven, Belgium; [4]Revision Implant NV, Leuven, Belgium

Abstract: Visual cortical prostheses have advanced substantially over recent decades, yet the mechanisms by which intracortical microstimulation shapes perception remain incompletely understood. Moreover, the effects of monopolar (between an electrode and a remote reference) and bipolar (between two intracortical electrodes) stimulation on cortical neuronal responses have not been systematically assessed. Here, we investigated how different electrical stimulation configurations modulate neuronal responses in early visual cortex (V1 and V2). Neural activity was recorded from V1 and V2 in three awake rhesus macaque monkeys implanted with thin, flexible intracortical electrode arrays during a passive fixation task. Electrical microstimulation was delivered using either monopolar or bipolar configurations (200 Hz, 200 ms) at 10 to 110 μA. We calculated a modulation index as MI = ((BP - MP1) / (BP + MP1) + (BP - MP2) / (BP + MP2)) / 2, in which BP = bipolar stimulation and MP1 and MP2 = monopolar stimulation. Among electrodes with excitatory responses (N = 959 over 141 recordings), 40% of bipolar responses were explained by one or both corresponding monopolar conditions (MI between 0 and 0.5; range: 35-44%). In 34% of responsive electrodes, monopolar stimulation elicited stronger responses than bipolar stimulation (MI < 0; range: 14-46%). Importantly, a substantial proportion of responsive electrodes (26%) exhibited bipolar facilitation that could not be accounted for by either monopolar condition alone (MI > 0.6; range: 18-41%). The effects of stimulation configuration (monopolar versus bipolar) depended strongly on stimulation intensity, influencing both the magnitude and temporal profile of neuronal responses. Furthermore, neural modulation was frequently observed on electrodes located far from the stimulation site, indicating that the spatial pattern of activation across non-stimulated electrodes could not be reliably predicted based solely on their distance from the stimulated electrodes. Together, these results demonstrate that intracortical microstimulation elicits diverse and spatially distributed neuronal modulations in V1 and V2, with both intensity- and configuration-dependent effects, including bipolar facilitation.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Program #/Poster #: PSTR097.24/Y16

Topic: E.06. Vision

Support: NIH R01-EY014882 to H-KL.

Title: Rapid emergence of oscillatory activity in the primary visual cortex of adult-enucleated mice

Authors: *L. MESIK[1], H. PHAM[1], H.-K. LEE[2];
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Abstract: In the absence of sensory inputs, the cortex does not turn silent but instead remains spontaneously active. We have recently investigated how this spontaneous activity changes following complete loss of vision and noticed a rapid increase in oscillatory activity within the primary visual cortex (V1) after enucleation. To investigate these oscillations further, we used local field potential (LFP) recordings to confirm that these oscillations are confined to V1, with no apparent spillover into the primary somatosensory cortex (S1) and are most prominent in the 0.1-8Hz frequency range, covering slow oscillations, delta and theta bands. They were strongest 1 day after enucleation, weakening in the following week but remaining higher than the pre-enucleation baseline recorded in complete darkness. The oscillations were generally suppressed by mouse activity and whisking, and we are currently exploring potential mechanisms of this suppression. To check whether these oscillations could be inherited from the thalamus- as opposed to being generated within V1- we performed fiber photometry in the lateral geniculate nucleus (LGN) with or without V1 inhibition. Within LGN, we observed a marked increase in spindle-like 5-6Hz oscillatory events following enucleation. However, inhibition of V1 completely abolished this activity, suggesting that while LGN may contribute towards V1 oscillatory activity, it does not appear to produce it independently of V1. Our results indicate that after complete loss of retinal inputs, the visual cortex generates spontaneous activity dominated by low frequency oscillations, which can be transiently abolished during periods of alertness.

Disclosures: L. Mesik: None. **H. Pham:** None. **H. Lee:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Topic: E.06. Vision

Support: NIH R00MH116100
NSF-2449277 Career Grant (AMB)
Vanderbilt Startup Funds (AMB)

Title: Inhibitory mechanisms of alpha/beta oscillation in predictive processing

Authors: *Y. XIONG[1], K. GABHART[4], H. NEJAT[2], A. BASTOS[3];
[2]Psychology, [3]Psychology and Vanderbilt Brain Inst., [1]Vanderbilt Univ., Nashville, TN;
[4]Columbia Univ., New York, NY

Abstract: Alpha/beta (8-30Hz) oscillatory activity has been linked to various higher-order cognitive functions such as attention and working memory. Such oscillations are found be inversely related to spiking activity, and are hypothesized to have inhibitory functions which aid in cognitive functions. Here I investigate the mechanism of this inhibitory function. I present results from a no-report local/global oddball paradigm recorded across multiple cortical areas (V4,TEO,MT, MST, FEF, PFC) in macaque monkeys, leveraging optogenetic tagging of inhibitory interneurons to obtain ground-truth cell type identification and guide putative classification of excitatory and inhibitory cells. Contrary to the hypothesis that alpha/beta exerts inhibitory control by directly upregulating inhibitory cell firing, inhibitory cells did not show increased spiking during high alpha/beta states. Both inhibitory and excitatory cells increased firing in response to oddballs. Instead, alpha/beta exerts its inhibitory influence through a phase-locking mechanism: during predictable stimuli, inhibitory cells (but not excitatory cells) showed significant increase in phase locking to alpha/beta. Furthermore, the phase at which inhibitory cells locked to alpha/beta significantly predicted their oddball encoding strength, but not in inhibitory cells. These findings suggest a strong role of inhibitory cell in predictive processing, as well as top-down alpha/beta inhibition.

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Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Program #/Poster #: PSTR097.26/Y18

Topic: E.06. Vision

Support: NEI R010005911

Title: Increases of cortical neuron spike rate guide behavior more effectively than equivalent spike rate decreases

Authors: *L. WEI, J. H. R. MAUNSELL;
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Abstract: How the brain translates changes in cortical spike rates into behavior remains a fundamental question in systems neuroscience. Although increases and decreases in spike rate can, in theory, convey equivalent amounts of information, recent optogenetic studies in mouse V1 have revealed a striking asymmetry: mice readily detect spike rate increases but are insensitive to equivalent decreases (Cone et al., 2020).
To test whether this asymmetry extends to primates, we trained rhesus monkeys to detect changes in the motion coherence of dynamic random dot stimuli. While the monkeys performed the task, we recorded from individual neurons in the middle temporal visual area (MT), a key region for motion processing. Stimulus parameters (location, size, speed, and drift direction) were tailored to each neuron's preferences. MT neurons responded more strongly to high coherence than to low coherence when the dots drifted in their preferred direction.
We compared behavioral sensitivity to coherence steps with neuronal sensitivity, using receiver operating characteristic (ROC) analysis of spike rate changes. For coherence increments in the preferred direction, the neurometric sensitivity of MT neurons aligned with the monkey's psychometric thresholds (mean neurometric threshold (SEM): 23.8% (1.3%) coherence, mean psychometric threshold 21.2% (1.0%) coherence, n = 75 neurons). For coherence decrements, however, behavioral performance was markedly worse than neurometric performance (neurometric threshold: -30.0% (1.3%) coherence, psychometric threshold -41.1% (1.3%) coherence). Instead, the monkey's performance matched the neurometric sensitivity of neurons that preferred the opposite direction (threshold -41.0% (1.8%) coherence). These neurons increased their firing in response to coherence decrements, although their response modulations were always smaller than those of neurons that preferred the dot drift direction.
This correspondence suggest that detection depends predominantly on neurons that increase their spike rates, even when other neurons show larger spike rate decreases. This asymmetric readout highlights a fundamental constraint on which cortical signals can guide behavior.

Disclosures: L. Wei: None. **J.H.R. Maunsell:** None.

Poster

PSTR097: Visual System: Responses During Behavior and Response Modulation

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Program #/Poster #: PSTR097.27/Y19

Topic: E.06. Vision

Support: NIH NEI EY07977
EY035085
EY035838

Title: Perception of material affordances: possible roles of spatial statistics

Authors: *Y. XU[1], M. M. CONTE[3], J. D. VICTOR[3], Q. ZAIDI[2];
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[3]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY

Abstract: Anticipating affordances of a material such as slipperiness, ripeness, hardness or warmth from just its visual appearance is often necessary for using it appropriately. Studies of material properties, e.g. gloss, have concentrated on local perceptual cues such as highlights, but visual identification of some fabric qualities can be based on specific spatial-frequency bands (Giesel & Zaidi, 2013), suggesting that second- and higher-order spatial statistics may also be relevant. To investigate this possibility, we studied visual perception of fabrics varying widely in appearance and affordance.
We took high resolution photographs from a fixed distance of 80 flat fabric swatches, including most types of single-yarn woven, knit, braided, bonded and felted materials. 12 observers binocularly viewed the high-resolution grey-level images on a monitor and rated materials along 5-point scales over 10 opposing affordances: soft/rough, warm/cool, stiff/flexible, sturdy/delicate, water-absorbent/repellent, shiny/matte, see-through/opaque, smooth/coarse, elastic/rigid, thin/thick, in a block design. Within each affordance pair, we analyzed the images for which 5 or more observers chose the same rating.
The combined 10 dimensions of the discrete rating scales were subjected to dimensional reduction with a correspondence analysis (CA). Along CA1 (58.5% variance), the affordances fell in two groups: soft, smooth, water-absorbent, flexible, thin, delicate, cool, elastic, see-through, and shiny with negative weights and matte, opaque, warm, sturdy, thick, rigid, stiff, coarse, water-repellent and rough with positive weights. Weights along CA2 (14.5% variance) ordered the two groups from top to bottom in the order above, so the lines connecting opposing affordances show which pairs are closely related.
Fourier analysis showed significant correlations of roughness, warmness, stiffness, sturdiness, coarseness, rigidity and thickness ratings with distinct but overlapping spatial frequency bands (5-18 cyc/deg) corroborating the earlier results. Aiming for more specific identification, we computed local image statistics from the whitened and binarized images at multiple scales of down-sampling. Correlations with 2nd to 4th order statistics at specific scales supplemented the Fourier analyses in differentiating between affordances. It is possible that spatial frequency bands capture the scale of shape-from-shading in the images, while higher-order statistics can capture more complex 3D texture features. These texture features may be more specific for surface properties and may evoke memories of fabric classes during rating judgements.

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Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.01/Y20

Topic: E.06. Vision

Support: ANR-23-CE37-0016

Title: Neural mechanisms of unfamiliar face identity recognition in macaques revealed by fMRI frequency-tagging

Authors: *C. GISLOT[1], M.-A. LAURENT[2], B. ROSSION[3], J.-B. DURAND[4], B. R. COTTEREAU[5];
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Abstract: Face recognition is a cornerstone of human social interactions, providing essential information for identifying conspecifics. To investigate the neural mechanisms underlying face identity recognition (FIR) in a monkey model, we employed a frequency-tagging fMRI paradigm based on fast periodic visual stimulation (FPVS). Functional MRI data were collected from three rhesus macaque monkeys. Natural images of a single unfamiliar face identity, either human or monkey, were presented in a rapid visual stream at 6 Hz under two experimental conditions: (1) repeated presentation of the same face image, with only low-level visual variations in size, luminance, and contrast; and (2) presentation of different images of the same identity, exhibiting substantial natural variability in background, head orientation, and gaze direction. Every 9 s, a 2-s burst of seven images depicting different unfamiliar identities from the same species was inserted into the stream. These oddball identities were also presented with natural variations in background, head orientation, and gaze direction and alternated with images of the repeated identity. For each monkey and condition, 20 runs of 243 s (27 × 9 s cycles) (10 runs with monkey faces and 10 with human faces) were acquired with upright faces and 20 with inverted faces. Analyses were performed within face-selective regions (defined with a frequency-tagging localizer) and in the Fourier domain, where FIR responses were objectively identified and quantified at the identity change frequency peak (1/9 s = 0.111 Hz). Robust face discrimination responses (Z-scores > 2) were observed in all face-selective regions (PL, ML, MF, AL, and AF) in both hemispheres of all three animals for upright faces in the first condition. In the same condition, responses were significantly reduced for inverted faces (paired t-test, corrected for multiple comparisons) in anterior face patches (AL and AF), suggesting that these higher-level areas contribute to holistic face processing. However, FIR responses in all face patches were substantially reduced in Condition 2, revealing a limited capacity of the macaque face-processing network to maintain identity representations across substantial image variations. Overall, our findings suggest that the macaque face-patch system is predominantly sensitive to face identity changes when these coincide with natural image variations, whereas responses are virtually abolished when such higher-level variations are controlled.

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Poster

PSTR098: Higher Visual Areas

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.02/Y21

Topic: E.06. Vision

Title: Immersive visual display systems for experimental neuroscience

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Abstract: Traditionally, vision has been studied using paradigms in which isolated and simplified visual stimuli are presented at or near the center of a flat display during visual fixation. This approach reduces the contribution of uncontrolled stimuli and self-directed movements, thus allowing one to estimate the visual parameters being represented by neurons or neural populations. However, much of vision is continuous, immersive, geometric, and active. To address these less explored aspects of vision, we developed two novel, immersive visual display systems, “domes”, for the presentation of naturalistic visual stimuli over a 180-degree panoramic display. One of these, a back-projected hemispheric dome that fits inside an MRI scanner bore, is designed for fMRI experiments in the awake macaque. The other, a large front-projected hemispheric display that uses a spherical mirror, is designed for macaque electrophysiology experiments. To achieve faithful angular visual geometry of both natural and artificial stimuli, we developed a software platform to adapt full-field videos, isolated stimuli, and virtual rendered environments to the dome displays. We have also developed a novel method that accounts for non-isotropic image-wide distortions in the image projection pipeline and warps the stimuli accordingly and ensures correct geometry of projected stimuli. Pilot fMRI experiments demonstrate the strong activation of peripheral regions of the visual cortex using full-field dome stimulation, both with conventional stimulus presentation and immersive first-person movement through a natural scene. The immersive dome environment is a powerful and adaptable framework for a range of visual neuroscience experiments, allowing for the systematic investigation of fundamental but infrequently studied aspects of everyday vision.

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Poster

PSTR098: Higher Visual Areas

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.03/Y22

Topic: E.06. Vision

Support: Department of Defense, through the Vision Research Program (VRP) under Award No W81XWH1910853

Title: Higher-order visual andattentional connectivity patterns revealedthrough naturalistic-viewing

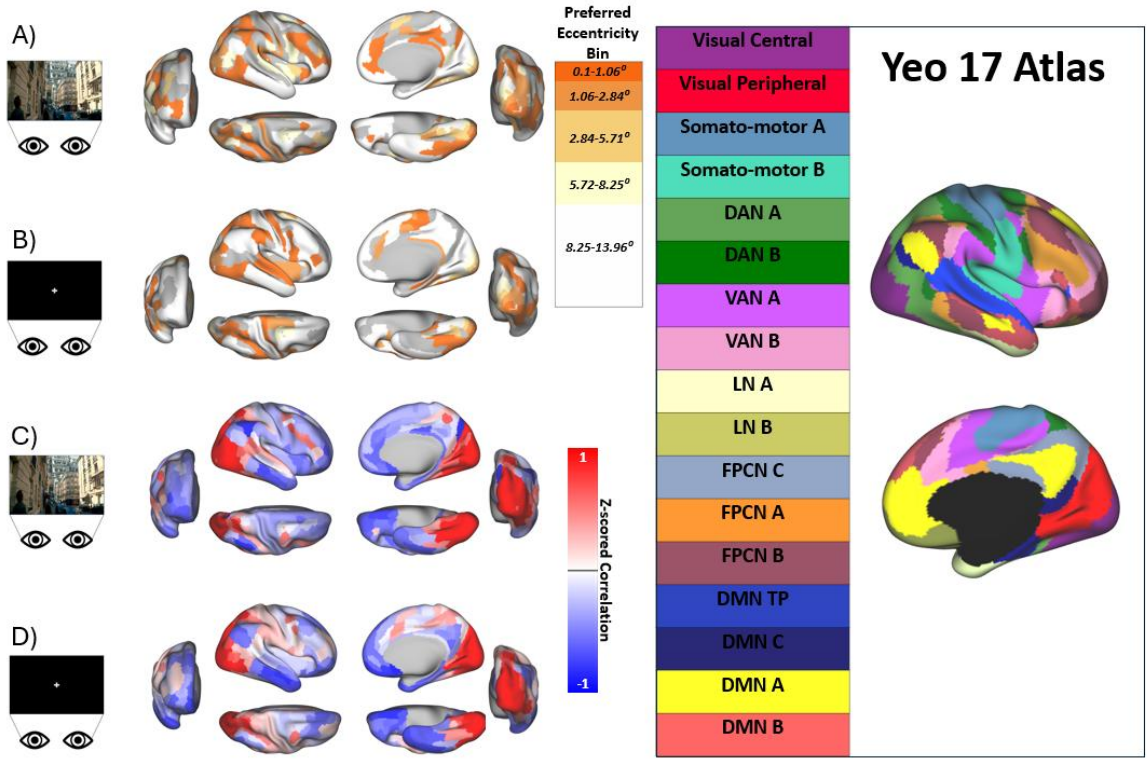
Authors: *A. COOPER[1], J. D. MENDOLA[2];
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Abstract: The retinotopic organization of the visual cortex provides a powerful framework for examining how spatial representations across the visual field interface with large-scale cortical networks. While there are unique global connectivity patterns across the eccentricity range of visual cortex, the impact of naturalistic viewing (NV) on these patterns has yet to be directly characterized.

Using 7T Human Connectome Project fMRI data, we compared resting state (RS) and NV conditions to determine how ecologically valid inputs modulate static, dynamic, and intersubject synchronization of functional connectivity across higher-order visual processing regions and beyond.

NV revealed enhanced local and global organization, strengthening the spatial precision and reliability of eccentricity-based coupling. Within higher-order visual processing regions, the motion-sensitive human middle temporal region emerged as a central hub, exhibiting the largest reduction in between-subject variability, the greatest increase in dynamic connectivity, and the highest intersubject correlation across participants. Beyond the visual cortex, NV revealed robust differentiation among higher-order attentional and control systems. Foveal representations showed increased positive connectivity with the frontoparietal control and dorsal attention networks, while exhibiting stronger negative coupling with ventral attention and cingulo-opercular systems. These networks were differentiated in terms of stimulus-driven activity, providing evidence for distinct roles in visual attention.

Overall, by integrating static connectivity, sliding-window dynamics, and intersubject correlation, this study demonstrates that naturalistic viewing refines the intrinsic retinotopic scaffold observed at rest and reveals its embedding within the brain's global attentional hierarchies. Eccentricity emerges as a unifying spatial axis linking sensory representation to control networks, showing how naturalistic perception reorganizes cortical communication across scales.



Disclosures: A. Cooper: None. **J.D. Mendola:** None.

Poster

PSTR098: Higher Visual Areas

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Indian Institute of Science internal grants
Google Asia Pacific research grant
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Research grant from CynLr
MoE fellowship, Govt of India

Title: Contextual modulation of feature positions in monkey inferior temporal cortex

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Abstract: Humans can discriminate small offsets between nearly collinear lines, a phenomenon known as vernier acuity. However, the underlying neural basis of this phenomenon is not fully understood. We investigated the neural basis of such effects through behavioral testing on monkeys and neural recordings from their inferior temporal (IT) cortex, an area critical for object recognition. We created stimuli containing a square frame with a circular disk that could be moved along a horizontal or vertical line, in the presence of a horizontal or vertical bar at the center of the stimuli. The hypothesis is that if the monkey experiences the vernier effect, it could detect small horizontal shifts in the presence of a vertical bar (near context) rather than in the presence of a horizontal bar (far context). Likewise, it could detect small vertical shifts in the presence of a horizontal bar (near context) and not in the presence of a vertical bar (far context). We tested these predictions in behavior, on monkeys performing a same-different task, as well as in neurons, using brain recordings from IT cortex. In the same-different task, monkeys detected small position shifts in the near context for both horizontal and vertical position shifts of the circular disk. This behavioural result suggests that small shifts are far apart or dissimilar in perceptual space; hence, we reasoned that we should see greater neural dissimilarity in the near context. Using neural activity from a passive fixation task, we computed the average neural distance between stimuli in the near and far contexts. Here, too, we observed greater neural dissimilarity between the stimuli in the near context compared to the far context. Interestingly, this effect arose late in the neural response, suggesting that it arises through computation and is not simply inherited from early visual areas. This effect was driven by neurons that showed modulation to position and context, and with interactions between position and context. Taken together, our results show that monkeys show contextual modulation of feature position just like we do, and that the possible neural basis for this effect resides in their inferior temporal cortex.

Disclosures: S. Simon: None. **S.P. Arun:** None.

Poster

PSTR098: Higher Visual Areas

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.05/Y24

Topic: E.06. Vision

Support: Whitehall Foundation

Title: Cortical folding anchors locations of retinotopic maps in the primate intraparietal sulcus

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Abstract: Across the visual system, functional areas often occupy predictable positions relative to cortical folds, suggesting that local morphology provides anatomical landmarks for areal organization. The intraparietal sulcus (IPS) offers an informative case for examining this

relationship across primates, since humans and macaques share a broadly similar set of retinotopic maps that fall along the IPS. Despite this similar functional organization, human posterior parietal cortex is greatly expanded and more convoluted compared to macaques. Here, we compared retinotopic map organization, folding variability, and local convexity landmarks in human and macaque IPS to determine how these conserved maps are positioned within species-specific cortical anatomy. To characterize IPS retinotopy and local folding patterns, we analyzed structural MRI data from 63 humans and 17 macaques, along with fMRI retinotopic data from 44 humans and 6 macaques. Retinotopic maps were projected to species-specific average template surfaces to assess their spatial arrangement and interindividual overlap. Cortical folding was quantified using surface convexity measures, allowing us to identify recurring convexity peaks, or "bumps," along the banks of the IPS and evaluate their spatial relationship to retinotopic maps. In both species, maps were arranged primarily along a posterior-to-anterior axis, but their position relative to the sulcus differed. Macaque maps occupied the lower bank of the IPS, whereas human maps occupied the upper bank. After template alignment, map overlap across individuals was greater in macaques than humans, indicating greater variability in human map locations. Convexity analyses further revealed substantially greater variability in human IPS morphology. Despite this variability, both species exhibited recurring convexity peaks along the upper and lower banks of the IPS and in the posterior IPS. Although individual bumps did not show a strict one-to-one correspondence with individual retinotopic maps, maps nonetheless occupied predictable positions relative to these folding landmarks, indicating that local IPS morphology remains systematically related to functional organization despite substantial expansion of human posterior parietal cortex. Similar IPS bumps were also observed in fetal macaques and across other primate species, suggesting that these landmarks reflect conserved features of primate cortical folding that may help scaffold the organization of visual maps across development and evolution.

Disclosures: R.N. Sathishkumar: None. **K.S. Weiner:** None. **M.J. Arcaro:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

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Program #/Poster #: PSTR098.06/Y25

Topic: E.06. Vision

Title: Perceptography of face-selective neurons

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Abstract: Perceptography is a recently introduced paradigm that visualizes complex perceptual distortions elicited by local brain stimulation. In this approach, machine-learning methods iteratively use high-throughput behavioral data to optimize image distortions until they become difficult for the animal to distinguish from the percepts evoked by cortical stimulation. In earlier

work, we used optogenetic stimulation, which established the basic concept but did not include simultaneous recordings from the stimulated neurons. In the present study, we extend perceptography by combining stimulation and neural recording from defined neuronal populations in the inferior temporal (IT) cortex, including face-selective neurons. Two Utah arrays were implanted, one targeting the middle face patch and the other central IT cortex. Macaque monkeys were trained on a cortical stimulation detection task in which they maintained fixation on a computer-generated image for 1 s; halfway through this interval, the image was altered for 200 ms, and in 50% of trials, an electrical stimulation train (200 ms) was delivered at random. Following image offset, two choice targets appeared, and the animals reported whether stimulation was present for liquid reward. This approach yielded, for the first time, perceptograms derived specifically from face-selective populations, in which stimulation of the middle face patch produced face-related distortions that differed systematically from those evoked by stimulation of the neighboring cortex. Stimulation on the face patch mostly produced perceptograms for face stimuli, while stimulation of the out-of-face patch produced perceptograms from both face and non-face stimuli. Furthermore, face distortions that emerged during face-patch stimulation appeared only contralateral to the stimulated hemisphere, while stimulation outside the face-patch produced whole-image distortions for both face and object seeds.Simultaneous neural recordings supported this pattern: contralateral distortions or presentations evoked stronger responses in face-selective neurons for face stimuli, whereas outside the face patch, central bilateral image distortions elicited the largest responses for both face and object stimuli.

Disclosures: S. Ledet: None. **D. Nguyen:** None. **E. Shahbazi:** None. **A. Afraz:** None.

Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.07/Y26

Topic: E.06. Vision

Support: ZIA MH002909
ZIA EY000511

Title: Mapping shared representational structure between macaque and human cortex using cross-species hyperalignment

Authors: *K. BRAUNLICH[1], M. DUYCK[3], C. I. BAKER[2], B. R. CONWAY[4];
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Abstract: Functional homologies between human and macaque cortex remain incompletely understood, reflecting both methodological differences across species and limitations on shared behavioral paradigms. We propose that cross-species hyperalignment using naturalistic stimuli

provides a powerful framework for addressing this challenge. Naturalistic stimuli engage diverse perceptual and cognitive processes while requiring minimal training, enabling data-driven identification of shared multivariate representational structure. An obstacle for cross-species fMRI is that humans are typically scanned using BOLD contrast, whereas macaques are commonly scanned using monocrystalline iron oxide nanoparticles (MION), which improves signal-to-noise ratio but exhibits a distinct hemodynamic response. To address this challenge, we developed Multiview Temporal Alignment (MVTA), a novel approach that learns transformations aligning MION timecourses to BOLD, enabling cross-species hyperalignment and direct cross-species translation of experimental insight. We applied this framework to a deep cross-species dataset comprising approximately 104 hours of naturalistic fMRI data from each of three macaques and 2.3 hours from each of nine humans. Analyses of retinotopically defined visual areas (V1-V4) revealed substantial preservation of representational organization across species, including preserved hierarchical structure and area-specific representational fingerprints. However, we also identified a systematic hierarchical asymmetry whereby higher-order macaque visual areas were more similar to lower-order human visual areas, an effect that was amplified during movie viewing relative to temporally synchronized static image sequences. Full brain analyses revealed strongest correspondence in visual and temporal cortex and reduced correspondence in regions associated with disproportionate human cortical expansion. Cross-species searchlight analyses further identified candidate homologues beyond early visual cortex (including brain regions associated with theory of mind). Together, these findings demonstrate conserved representational patterns while revealing systematic evolutionary shifts in cortical representation.

Disclosures: K. Braunlich: None. **M. Duyck:** None. **C.I. Baker:** None. **B.R. Conway:** None.

Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.08/Y27

Topic: E.06. Vision

Support: NIH Grant EY022428
Simons Foundation

Title: Neuronal correlates of visual masking in macaque V4

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Abstract: The stimulus specificity and time course of visual masking are useful probes of mechanisms that shape visual response. In association with behavioral measurements of forward and backward visual masking, we have studied responses in single neurons recorded from V4 of awake fixating macaques. We are specifically interested in how masking affects the coding of

natural image statistics, so we used texture stimuli created with the method of Portilla & Simoncelli [Int J Comp Vis, 2000] to control those statistics while holding low level image features constant. We stimulated neuronal receptive fields with briefly flashed test targets presented between 0 and 200 ms before or after a 100 ms texture mask. The test and masking targets could be either naturalistic textures (T) or phase-scrambled noise (N). Responses to leading test targets were uninfluenced by the mask. Responses to following test targets were diminished at short intervals and recovered progressively at longer ones. The magnitude and time course of suppression varied across neurons, suggesting diversity in the underlying mechanisms. Most neurons preferred T test targets to N ones, but the effects of masking were largely similar for both. Curiously, responses to T test targets were often enhanced for delays of ~100 ms, compared to responses to N test targets. We fit a delayed divisive normalization model to neuronal responses [Zhou et al., PLoS Comp Biol, 2019]. The model captured both stimulus selectivity (T vs N) and suppression across delays. The dynamics of normalization varied across neurons, capturing the diverse time course of suppression. We explain forward masking as a consequence of a decaying divisive normalization signal generated by preceding stimulation. When a second stimulus arrives while normalization remains elevated, responses are suppressed; as normalization decays, responses recover. No similar explanation can be found in our data for backward masking, which must arise from other mechanisms. The model in simple form also does not explain the enhanced recovery from suppression for T but not N test targets. Our findings suggest that delayed divisive normalization can provide a mechanistic account of forward - but not backward - visual masking in V4. More broadly, the results indicate that delayed normalization not only controls response gain in the face of variations in visual stimuli, but also determines how the visual system integrates information across time.

Disclosures: L. Palmieri: None. **J.A. Movshon:** None.

Poster

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Indian Institute of Science internal grants
Google Asia Pacific research grant
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Title: Natural image reconstruction from a compact population of Inferior Temporal cortex neurons

Authors: *S. BHARADWAJ[1,2], G. JACOB[2], S. P. ARUN[2];
[1]Univ. Paris Cité, Paris, France; [2]Ctr. for Neurosci., Indian Inst. of Sci., Bangalore, India

Abstract: Reconstruction of images from neural activity has been a longstanding goal in vision research, but previous research has only focused on obtaining reconstructions using whole brain recordings (fMRI/EEG/MEG) or electrode arrays that span the visual cortex. Thus, it remains unclear whether natural images can be reconstructed faithfully from a small population of neurons from a single brain region. To investigate this issue, we recorded neural activity from microelectrode arrays implanted in the inferior temporal (IT) cortex of two macaques (256 channels) in response to 11,216 images (10.2k natural images + 1016 images for 16 Out-of-Distribution (OOD) categories). We reconstructed these neural responses by mapping them to the latent vectors of several pretrained generative models - three 1D VQ tokenizers (TiTok, One-D-Piece, FlexTok), two GANs (ResNet-BigGAN, StyleGAN-XL), and CLIP-text guided Stable Diffusion. Using rigorous quantification, we showed that these reconstructions are not just broad category decoding enhanced by generative priors: a few hundred IT neurons contain sufficient information to reconstruct images, capturing both categorical and low-level stimulus features like color, shape, size and orientation. We also showed that the choice of generative model is critical to produce reliable non-spurious reconstructions, with our 1D tokenizer and ResNet GAN based pipeline outperforming StyleGAN-XL and Stable Diffusion pipelines used in previous state-of-the-art work. Testing these models on OOD categories, we found that the extent of generalization decreases with distance from the training set; truly novel patterns of activity were not reconstructed. Finally, we quantified how reconstruction scales across neuron counts, training-data-size and repeats, obtaining distinguishable reconstructions using neural data from less than a hundred neurons, or a single repeat, or using a few hundred training images. Taken together, our results demonstrate that natural images can be reconstructed reasonably well from small populations of neurons in the high-level visual cortex.

Disclosures: S. Bharadwaj: None. **G. Jacob:** None. **S.P. Arun:** None.

Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.10/Y29

Topic: E.06. Vision

Support: MWU Faculty Start-up Grant 11-4080-1978-9656
MWU Intramural Grant 10-2018-8138

Title: tRNS Selectively Excites Sensory but Not Oculomotor Visual Pathways: A Dissociation in Amblyopia and Convergence Insufficiency

Authors: *R. AKHAURY[1], K. VAN[1], K. HALL[4], K. DECKER[2], A. QUAN[3,5,6], A. CHAKRABORTY[3,7];
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[6]Feinberg Sch. of Med., Northwestern, Chicago, IL; [7]Sch. of Optometry and Vision Sci., Univ. of Waterloo, Waterloo, ON, Canada

Abstract: Purpose: Transcranial random noise stimulation (tRNS) is recently gaining popularity to treat sensory aspects of visual deficits. However, its efficacy in treating oculomotor deficits is currently unknown. Functional MRI implicates distinct neural substrates for sensory and oculomotor deficits, involving reduced activation in sensory areas such as V1 and MT+ in amblyopia, versus similar deficits in oculomotor centers such as the frontal eye field and cerebellum in convergence insufficiency (CI). In this study, we compared the efficacy of tRNS in patients with amblyopia and CI.
Methods: Two randomized, sham-controlled ongoing study cohorts were combined for this analysis. Cohort 1: 16 adults with amblyopia (27 ± 7y) underwent baseline phosphene threshold (PT) mapping via transcranial magnetic stimulation, then 5 consecutive daily sessions of active tRNS (1 mA, 100-640 Hz, 40 min over primary visual cortex) or sham. PT, crowded visual acuity, contrast sensitivity, and stereoacuity were assessed before/after each session and at 24-h, 72-h, and 10-day follow-up. Cohort 2: 15 adults with CI (25 ± 2y) completed 8 sessions over 4 weeks, spaced 48h apart for washout, receiving active tRNS (1 mA, 30 min over left frontal eye field and cerebellum across separate sessions) or sham (0 mA). Near point of convergence and fusional vergence amplitudes were measured before/after each session.
Results: In amblyopia, tRNS increased cortical excitability along the sensory pathway: PT fell daily (pre-day1 vs. post-day5: 21 ± 9%), persisting at 24 h ($p < 0.001$) and 72 h ($p = 0.001$-0.005) but diminishing by 10 days in most patients. In CI, tRNS produced no significant change in oculomotor function. None of the sham stimulation sessions showed any modulatory effect in amblyopia or convergence insufficiency.
Conclusions: tRNS dissociates sensory and motor visual functions, selectively exciting sensory pathways while leaving oculomotor pathways unaffected. This underscores the need for region- and network-specific stimulation rather than a single protocol. Future work should compare tRNS, tACS, and tDCS in the same populations and explore multimodal stimulation strategies to optimize visual rehabilitation.

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Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.11/Y30

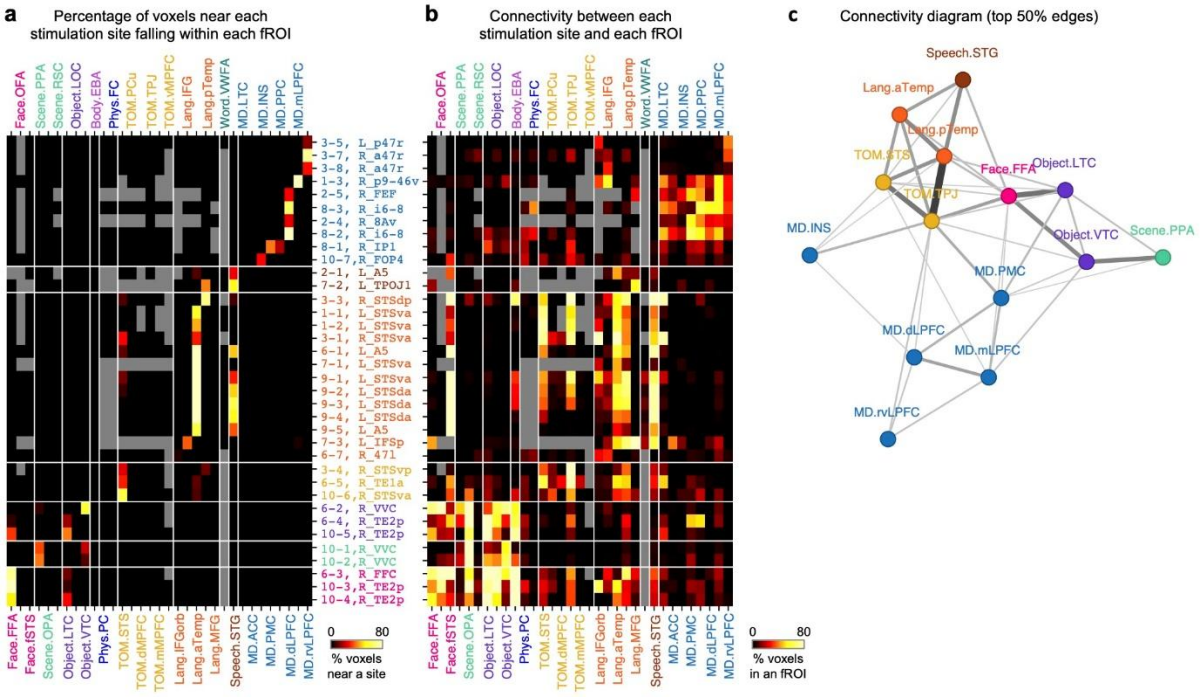
Topic: E.06. Vision

Title: Monosynaptic connections link functionally similar regions in human cortex

Authors: *R. XU[1], A. BUSH[2], A. TAKAHASHI[1], N. SISTERSON[2], A. WALTON[2], S. HUTCHINSON[1], A. KAMMEN[2], C. NEUDORFER[2], V. KOKKINOS[2], P. NANDA[2], N.

JHINGAN[1], A. MARVI[1], A. FUNG[1], S. DURAIVEL[1], E. HOSSEINI[1], C. CASTO[1], C. VALENZUELA[1], S. YEE[3], J. KIRSCH[4], E. FEDORENKO[1], N. G. KANWISHER[1], R. DESIMONE[1], M. RICHARDSON[2];
[1]MIT, Cambridge, MA; [2]Functional Neurosurg., [3]Radiology, Massachusetts Gen. Hosp., Boston, MA; [4]Athinoula A Martinos Ctr. for Biomed. Imaging, Boston, MA

Abstract: The functional organization of human cortex has been mapped in considerable detail, yet the axonal connections linking these areas remain largely unknown. This gap precludes inferring either the computational pathways through cortical networks or the principles governing why each area connects to its particular target regions. Here, in patients undergoing intracranial monitoring for epilepsy, we used concurrent electrical stimulation and functional magnetic resonance imaging (es-fMRI), validated previously against tracer studies in nonhuman primates, to map anatomical connectivity of cortical sites across the whole brain, and combined these maps with task and resting-state fMRI in the same individuals. Es-fMRI revealed four main findings. First, connectivity followed an asymmetric functional-similarity principle: connected sites tended to share similar functional profiles, but, because connectivity is sparse, most pairs of functionally similar sites were not connected. Second, although connectivity also declines with distance, the functional profile explained three times as much variance in connectivity as distance did, and long-range connections were the most functionally specific. Third, es-fMRI revealed direct monosynaptic links between established functional regions, including between the fusiform face area (FFA) and the temporoparietal junction (TPJ) for social cognition. Fourth, resting-state functional connectivity (rsFC) of a stimulation site was only weakly correlated with that site's es-fMRI connectivity. Together, these results provide a first principled link between anatomical connectivity and functional organization in the human cortex, and establish es-fMRI as a scalable approach to building a tracer-grade connectome of the human brain.



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Poster

PSTR098: Higher Visual Areas

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Topic: E.06. Vision

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NSF CAREER 2143077 (CRP)
Packard Foundation (CRP)
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Hearst Fellowship (GRT)

Title: Receptive-field hotspots reveal the local features that drive primate high-level vision

Authors: *G. RAMOS-TRASLOSHEROS[1], C. R. PONCE[2];
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Abstract: Classical receptive fields define where a stimulus can influence a neuron, but not where the core computation occurs within that field. In convolutional networks, units learn nonuniform spatial weights that concentrate sensitivity into peaks, suggesting that a receptive field may contain a smaller hotspot that controls the response. We asked whether such hotspots also organize primate ventral visual cortex and whether they reveal the local features that drive high-level neurons.

Because high-level neural preferences may not align with intuitive image dimensions, we first tested whether neuronal tuning was apparent to human observers. In an odd-one-out task (~4,000 trials), 10 observers selected the outlier from image triplets ordered either by recorded neural tuning or by parametric dimensions. Observers performed well for contrast, spatial frequency, orientation, hue, and curvature (64.5-91.0%; chance, 33.3%), but were near chance for naturalistic preferences of biological (41.5%) and artificial (36.8%) units. This interpretability gap motivated a bottom-up approach in which neurons, rather than experimenters, specified the relevant features.

We therefore used closed-loop, GAN-based activity maximization in macaques with chronic arrays in V1, V4, and inferotemporal cortex. After optimizing images for individual units, we locally scrambled circular subregions to identify the image parts necessary for the response. Across areas, perturbing a single subregion was often sufficient to abolish activity, indicating that optimized responses were dominated by focal hotspots rather than by the full classical

receptive-field envelope. Presenting isolated hotspot features on unrelated natural-image backgrounds confirmed that these fragments were also sufficient to drive responses. The dominant features were contrast-defined motifs confined within the measured receptive field, rather than whole-object configurations. In a subset of units, removing surrounding image context increased responses above the full optimized image, suggesting that the hotspot can be gated by a suppressive surround. These results revise the receptive-field concept for high-level vision: the receptive field defines where a neuron can be influenced, but a smaller hotspot often determines what the neuron computes. Mapping these hotspots offers a tractable route from otherwise uninterpretable preferences to local visual mechanisms and suggests that ventral cortical selectivity is organized around dominant local features embedded within, and regulated by, the broader receptive field.

Disclosures: G. Ramos-Traslosheros: None. **C.R. Ponce:** None.

Poster

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Program #/Poster #: PSTR098.13/Y32

Topic: E.06. Vision

Support: NIMH ZIAMH002958

Title: Perceptography reveals color rich hallucinations from face selective neurons

Authors: *E. SHAHBAZI[1], S. LEDET[2], D. NGUYEN[3], A. AFRAZ[4];
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[4]NIH/NIMH, Bethesda, MD

Abstract: Perceptography is a recently developed paradigm that, for the first time, visualizes stimulation induced perceptual events, offering a general framework not restricted to a particular visual area and that could, in principle, extend to other sensory systems. By reconstructing what the animal “sees” from local perturbations in neural activity, perceptography helps close the causal gap between high level population responses and subjective perception and lays the conceptual groundwork for future visual prosthetics and mechanistic study of visual hallucination. Here, we apply this framework to the middle face patch and a neighbor neurons in IT cortex. We compare face perceptograms from this patch to those obtained from nearby, non face selective control regions using simultaneous electrophysiological stimulation and recordings in macaque monkeys Monkeys were trained to perform a cortical stimulation detection task. Trials began with fixation on a computer generated image, At the midpoint of the 1s presentation, we altered the image for 200ms and delivered Utah Array stimulation on 50% of trials at random for 200ms. After presentation, two targets appeared, and the animals indicated whether stimulation occurred; correct reports earned a liquid reward. We stimulated/recorded from channels inside and outside the middle face patch in IT cortexThis approach yielded, for the

first time, perceptograms of face selective neurons, revealing stimulation induced distortions of faces that were systematically different from those evoked by stimulation of neighboring IT cortex. Face selective sites in the middle face patch produced tightly localized shifts in perceived face position within the visual field and robust, color enriched distortions, even for achromatic base images, whereas non face selective IT sites predominantly induced shape and contrast based changes that largely preserved the stimulus' physical color profile, consistent with prior evidence that IT object representations emphasize shape and luminance over color. These effects were observed in both behavior and neural responses across channels inside and outside the patch, indicating a distinct organization of receptive space and chromatic processing for face selective populations within ITTogether, these data establish face perceptography as a powerful tool for causal interrogation of high level visual areas, suggest that the middle face patch implements a physiologically distinct encoding of visual space and color in the service of face representation, and open the door to systematic mapping of how face patches across IT cortex transform stimulation into vivid, category specific percepts

Disclosures: E. Shahbazi: None. **S. Ledet:** None. **D. Nguyen:** None. **A. Afraz:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.14/Z1

Topic: E.06. Vision

Support: Intramural Research Program of the NIMH (ZIAMH002958)

Title: Face neurons resist artificial perturbation while processing faces

Authors: *B. KARAMI, A. DINH, R. AZADI, A. AFRAZ;
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Abstract: We have established earlier that the behavioral detectability of optogenetic perturbation in macaque inferotemporal (IT) cortex varies with the characteristics of concurrently viewed images. It is not clear if this behavioral phenomenon reflects downstream readout filtering of the stimulation induced neural activity or a recurrent mechanism that resists perturbation. To differentiate between these hypotheses, we measured how neurons react to artificial perturbation while various images are being viewed. We recorded from and simultaneously perturbed 573 neurons in face-selective and neighboring IT regions of two macaques, targeting excitatory neurons transduced with pAAV-CaMKIIa-C1V1(t/t)-TS-EYFP. Optogenetic modulation during face and nonface conditions was quantified using a Perturbability Index (PI), defined as the difference in opto-evoked modulation between image-present and no-image conditions.Neurons in face-selective regions exhibited lower PI for faces than nonfaces, whereas this asymmetry was absent in nonface-preferring regions. This effect was not explained by a response ceiling, as the face-nonface perturbability difference (dPI) was unrelated to

optogenetic modulation magnitude (Spearman $\rho = 0.043$, $p = 0.368$).We next examined two population properties: faceness index, reflecting average neural preference for faces, and response homogeneity index, reflecting convergence of individual neurons in face-nonface response space. dPI was significantly predicted by both faceness index ($\beta = -3.20$, $p = 9.61e-11$) and response homogeneity index ($\beta = -9.58$, $p = 6.52e-22$), suggesting that collective population structure determines perturbability.To examine perturbation effects in neural state space, we applied PCA to population visual responses, defined a visual subspace using PCs explaining 85% of variance, and projected optogenetic perturbation vectors into this subspace and its orthogonal complement. For faces but not nonfaces, opto-evoked displacements were significantly smaller within the visual subspace ($p = 0.015$), suggesting that the natural face response manifold resists perturbation.Finally, we tested deep convolutional and recurrent neural network models on face-nonface differential perturbability. Only the recurrent network reproduced the key effect: faces were less perturbable than nonfaces when trained to achieve face selectivity.Together, these results support a recurrent mechanism in high-level visual cortex whereby the neural state evoked by a visual input determines resistance to perturbation: more stable, low-energy attractor states are harder to displace than less stable ones.

Disclosures: B. Karami: None. **A. Dinh:** None. **R. Azadi:** None. **A. Afraz:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.15/Z2

Topic: E.06. Vision

Support: NSF GRFP DGE-2146755
NSF 2547344

Title: Learning to generalize: The development of category and format representations in human visual cortex

Authors: *J. YAO[1], M. LINKA[1], K. DUCRE[1], K. GRILL-SPECTOR[2];
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Abstract: A central goal of visual neuroscience is understanding how children recognize objects of the same category across diverse visual formats. Ventral temporal cortex (VTC) supports object categorization through clustered and distributed representations. In adults, VTC responses to objects of the same category are similar across visual formats. However, it is unknown how category and format representations emerge across development. Using fMRI, we measured VTC responses in children (N = 6, ages 4-6), teens (N = 9, ages 14-17), and adults (N = 13, ages 19-34) to stimuli from 5 ecologically relevant categories (words, hands, faces, objects, places) presented in 3 formats (line drawings, emojis, photographs). As lateral and medial VTC have distinct functional properties and development, we analyzed them separately. We examined

category and format information in distributed responses using representational similarity matrices (RSMs), multidimensional scaling (MDS), and independent category and format classifiers. In lateral VTC, representations become organized by category with age. Child RSMs and MDS showed weak category structure, with category distinctions only for faces and hands and low within-category similarity across formats. Teen RSMs and MDS exhibited more distinct categories and increased within-category similarity across formats. By adulthood, lateral VTC RSMs and MDS showed high within-category similarity and tight clustering by category, indicating category generalization across formats. Category decoding in lateral VTC exceeded format decoding (50-60%) and increased across development (children: 54% ± 10%; teens: 84% ± 5%%; adults: 80% ± 10%). Medial VTC representations were organized by format, though category structure increased with age. Child RSMs and MDS showed format structure, with higher within than across format similarity generating distinctions between photographs, emojis, and drawings, and no category structure. Teen and adult RSMs and MDS showed stronger similarity and clustering by format and increasing similarity and clustering by category. Format decoding in medial VTC was stronger (62% ± 9%) than category (48% ± 13%) in children. In teens and adults, format (teens: 75% ± 8%, adults: 71% ± 8%) and category decoding (teens: 73% ± 7%, adults: 70% ± 9%) were similar. Overall, we find separable representations of category and format in VTC that continue to develop across childhood. These results suggest that the ventral stream supports generalization across formats yet maintains sensitivity to visual appearance, providing insight into how children learn and represent concepts across diverse visual forms and categories.

Disclosures: J. Yao: None. **M. Linka:** None. **K. Ducre:** None. **K. Grill-Spector:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.16/Z3

Topic: E.06. Vision

Support: HHMI
Simons Foundation: 543053

Title: The neural code for episodic experience in the primate hippocampus

Authors: *K. MOHAN[1], S. CHEN[1], J. LU[1], D. Y. TSAO[2];
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Abstract: Episodic memory - our subjective experience of *what* happened, *where,* and *when* - is organized as a sequence of discrete events rather than a continuous record of experience. This structure provides a powerful compression scheme that prioritizes behaviorally relevant information over the ongoing stream of sensory input. Episodic memory requires both the representation of individual events and the ability to link events into ordered experience. How

the hippocampus constructs such episodic representations remains unclear. Here, we identify a representational structure in the primate hippocampus that can directly implement both properties. We trained macaque monkeys to navigate a three-dimensional virtual-reality environment in which sequential object encounters unfolded within a rich spatial context while simultaneously recording hippocampal activity using *Neuropixels* probes. Individual hippocampal neurons exhibited robust selectivity for event identity and event order. At the population level, these variables were represented in separable dimensions, yielding a compositional code that factorized event content from temporal order within an episode. Replay-like events linked successive events through reinstatement of preceding event representations. These replay events transiently maintained information about past experience, providing a candidate mechanism for episodic memory formation. Together, these findings reveal how the primate hippocampus represents content and temporal structure of experience and links discrete events into episodic memory.

Disclosures: K. Mohan: None. **S. Chen:** None. **J. Lu:** None. **D.Y. Tsao:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.17/Z4

Topic: E.06. Vision

Support: Simons Foundaton
Howard Hughes Medical Institute

Title: The neural code for dynamic visual experience in the primate brain

Authors: *J. LU, K. MOHAN, D. Y. TSAO;
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Abstract: Vision does not unfold as a sequence of isolated images. In everyday life, the brain receives a continuous stream of input while the eyes move from one location to another, objects appear and disappear, and multiple people act at the same time. To understand such scenes, the visual system must determine what is present, where it is, which features belong together, how different objects relate to one another, and when the current interpretation of the scene should be updated. We recorded neural populations from inferotemporal cortex and ventrolateral prefrontal cortex while a monkey freely viewed a continuous social scene in which one or two characters entered, waited, interacted, and left. This design kept precise event labels while reducing the strong visual transients of discrete image presentation. The results showed a clear functional difference between the two regions. Inferotemporal cortex mainly represented the currently fixated face and updated rapidly after fixation changes. Ventrolateral prefrontal cortex integrated information across time and scene state, represented current and recently relevant identities, encoded entering and leaving events, and maintained identity information in different low-

dimensional formats depending on whether a person was fixated or not. It also carried a stable and largely identity-independent code for action category and action role across sessions. Together, these findings suggest that prefrontal cortex helps organize dynamic social scenes by combining context-dependent identity representations with a more general relational code.

Disclosures: J. Lu: None. **K. Mohan:** None. **D.Y. Tsao:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.18/Z5

Topic: E.06. Vision

Support: HHMI

Title: A temporal code for conscious perception

Authors: *J. K. HESSE[1], F. F. LANFRANCHI[2], C. MCGRORY[3], Y. SHI[4], T. A. ENGEL[5], D. Y. TSAO[6];
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Abstract: The neural correlates of consciousness remain elusive. Using binocular rivalry, previous studies found that higher-level cortex is weakly modulated by conscious percept, yet a pure signal of conscious perception has not been found anywhere in the brain. Here, we employed Neuropixels recordings across multiple face patches in inferotemporal cortex during a binocular flash suppression paradigm. We found that, during a constant stimulus and percept, the brain rapidly alternates, about 20 times per second, between conscious and suppressed micro-epochs. During conscious micro-epochs, a pure signal of conscious perception is present, allowing accurate reconstruction of the conscious image from neural activity. Conversely, during suppressed micro-epochs, a pure signal corresponding to the suppressed stimulus is present, supporting accurate reconstruction of the suppressed image.
Single cells showed ramp-shaped tuning to the conscious stimulus and no tuning to the suppressed stimulus during conscious micro-epochs. The opposite was true during the suppressed micro-epochs. Interestingly, tuning to the conscious stimulus during conscious micro-epochs was sharper than tuning to the suppressed stimulus during the suppressed micro-epochs, enabling differentiation of conscious and suppressed states. We found similar evidence for interleaved representations of conscious perception and suppressed stimuli in prefrontal cortex. Together, these findings suggest that the brain temporally multiplexes conscious perception with representations of unconsciously processed stimuli, and, speculatively, the neural correlates of consciousness may not reside in a specific place in the brain but rather a specific temporal phase.

Disclosures: J.K. Hesse: None. **F.F. Lanfranchi:** None. **C. McGrory:** None. **Y. Shi:** None. **T.A. Engel:** None. **D.Y. Tsao:** None.

Poster

PSTR098: Higher Visual Areas

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR098.19/Z6

Topic: E.06. Vision

Title: Face Sensitivity Across the Ventral Stream Hierarchy: A Comparison of Convolutional and Transformer-Based Vision Models

Authors: *N. THOMAS[1], M. BEYELER[2];
[2]Psychological & Brain Sci., [1]Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Neural networks are promising computational models of visual cortical processing, yet their biological similarity varies considerably across different networks. Brain-Score provides a benchmark for quantifying how well artificial neural networks predict neural responses across the ventral visual stream. Here, we compare two models: VGG16, a convolutional neural network, and a Vision Transformer (ViT), in their responses to intact, phase scrambled, and box scrambled human faces from the Olivetti dataset, and mean activation and selectivity index were extracted from model layers assigned to V1-, V4-, and IT-like stages using Brain-Score layer commitment data. VGG16 (Brain-Score: 0.125) showed higher responses to phase-scrambled than intact faces across examined layers, suggesting stronger sensitivity to local image statistics than face configuration. In contrast, ViT (Brain-Score: 0.377) transitioned from texture sensitivity at V1-like layers to face sensitivity at V4- and IT-like layers. These preliminary findings suggest that differences between CNNs and Transformers produce different activation patterns across model depth, with the higher Brain-Score model in this comparison showing response patterns more consistent with a hierarchical shift from low-level image sensitivity to intact-face sensitivity. Future work will extend this analysis to additional architectures, color face stimuli, and representational similarity analysis to better characterize intermediate visual representations in artificial vision models.

Disclosures: N. Thomas: None. **M. Beyeler:** None.

Poster

PSTR098: Higher Visual Areas

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Program #/Poster #: PSTR098.20/Z7

Topic: E.06. Vision

Support: NIH Grant DP2EY035176
Packard Fellowship - 2021-73455
NSF CAREER 2143077

Title: Temporal coding in the primate ventral stream

Authors: *C. A. KALINSKI[1], C. R. PONCE[2];
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Abstract: Humans and other primates move their eyes every few hundred milliseconds, bringing new visual input that must be processed before the next fixation. Within this brief interval, visual neurons exhibit rich firing dynamics that may reflect distinct stages of visual processing. Yet these dynamics are often obscured when neural responses are summarized as spike counts over a fixed post-stimulus window. This rate-based framework underlies much of systems neuroscience and is mirrored in standard convolutional neural networks, where units produce static activations via a feedforward pass. As a result, we lack a clear account of whether response dynamics are incidental consequences of neural biophysics or whether they reflect meaningful changes in feature encoding across time. Progress has been limited by the tight coupling between response magnitude and timing, making temporal response features difficult to manipulate independently. To address this, we used closed-loop, neuron-guided image optimization with multiple generative adversarial networks (GANs) while recording from neurons in primate visual cortex. On each generation, neural activity in a targeted temporal window guided the synthesis of future stimuli, allowing us to optimize images for distinct epochs of the same neuron's response. We first tested whether different image priors bias response timing by comparing two GANs: one that produced object-like, globally coherent images and another that produced more textural, locally structured images. Although both generators produced stimuli that strongly drove single neurons, object-like images preferentially evoked later responses, whereas texture-like images preferentially evoked earlier responses in the same neuron, even when average firing rates were matched. We next asked whether temporal response profiles could be shifted within a single image manifold by optimizing the same generator for early versus late response windows. This procedure successfully biased responses toward earlier or later firing patterns while maintaining similarly high average firing rates. Together, these findings show that temporal response structure can be dissociated from overall response magnitude and placed under closed-loop experimental control. More broadly, they suggest that response timing carries stimulus-dependent information that is lost in conventional rate-based summaries and may reflect different stages of feature encoding.

Disclosures: C.A. Kalinski: None. **C.R. Ponce:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.01/Z8

Topic: F.04. Voluntary Movements

Support: NIH/NINDS 5R37NS061963-17
NIH/NINDS 1R21NS135642-01

Title: Multi-area activity in mouse motor cortex associated with one-and two-handed oromanual dexterity

Authors: *J. M. BARRETT[1], J. I. GLASER[2,3,5], A. MIRI[4,5], G. M. SHEPHERD[1];
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Abstract: Cortical dynamics during goal-directed dexterous hand movements are mainly understood from paradigms involving use of the contralateral hand. To study how movement-related activity changes when the ipsilateral or both hands are used, we exploited a natural form of rodent manual dexterity - food handling - that rodents can perform uni- or bimanually. We sampled kilohertz 3D kinematics as mice used either or both hands to manipulate food, while recording spiking activity in multiple cortical areas. These included primary (fl-M1) and secondary (fl-M2) forelimb motor cortices. We also recorded in a lateral oral and manual (LOM) area, also known as tongue-jaw motor cortex, that has been implicated in oromanual food handling. Unit- and population-level analyses showed that activity in fl-M1 and fl-M2 depended on both laterality (ipsi- vs contralateral) and “manuality” (uni- vs bimanual), with few differences between the two areas. By comparison, activity in LOM was largely laterality- and manuality-invariant. These results demonstrate how activity in multiple areas of mouse motor cortex varies as the same task is performed unimanually with either hand or bimanually with both. Our findings support a model in which fl-M1 and fl-M2 maintain separable information about both forelimbs for bimanual coordination. Meanwhile, LOM encodes the distance from the mouth of the forelimb holding the food, an essential parameter for ingestion-related oromanual coordination.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.02/Z9

Topic: F.04. Voluntary Movements

Support: Frank and Evangeline Thompson Research Opportunity Fund
Steve Palermo Spinal Cord Injury Fund

Title: Motor cortex uses expanded neural dimensionality during reaching while preserving geometry

Authors: *X. SCHERSCHLIGT[1], A. G. ROUSE[2];
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Abstract: Introduction: Brain-computer interfaces can restore movement after neurological injury by recording neural activity and decoding intended behavior. Early work showed that motor cortical neurons often discharge as a function of movement direction. However, recent evidence shows that many neurons do not fit a simple direction model, motivating consideration of each neuron as a separate possible dimension in high-dimensional analysis. Biological network constraints restrict population activity from using the full neural space, yet it remains unknown how much motor cortex represents movement direction in a compact, task-like space or an abstract, higher-dimensional space. Therefore, we asked how many neural dimensions are required to best separate intended reach directions in primary motor cortex.

Methods: Two adult male rhesus macaques were implanted with four 32-channel floating microelectrode arrays in primary motor cortex and trained on a 16-target center-out reaching task. Broadband neural signals were spike sorted to identify action potentials from individual units, smoothed with a Gaussian kernel, and time-aligned to the task. For each session, trials were split using 5-fold cross-validation. Within each fold, training trials were averaged within target condition and used to build a PCA space. We selected the trial time sample that maximized neural distance between target conditions and projected individual trials at that time point into PCA space. To estimate population dimensionality, we trained 16-class linear discriminant analysis classifiers using progressively more principal components.

Results: Across 9 sessions each, Subjects A and B completed 7,004 and 8,355 trials, with 1,936 and 1,948 recorded M1 spiking units, respectively. Decoding accuracy peaked at 5.11 ± 2.76 (mean ± s.d.) dimensions for Subject A and 5.33 ± 1.66 dimensions for Subject B. Using the one-SE rule, performance plateaued earlier, at 4.44 ± 1.94 dimensions for Subject A and 4.11 ± 0.78 dimensions for Subject B. Confusion matrices showed decoder errors were not random; among misclassified trials, 52.8% in Monkey A and 47.9% in Monkey B were assigned to adjacent target directions, far above the 13.3% expected if errors were uniformly distributed across incorrect targets.

Conclusions: Decoding accuracy plateaued around 4 dimensions, approximately twice the dimensionality of the task space. Yet, the decoder errors demonstrate preserved local similarity of the circular task. This suggests a neural representation structured in M1 to maintain movement similarity but utilizing increased neural dimensionality compared to the task space.

Disclosures: X. Scherschligt: None. **A.G. Rouse:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.03/Z10

Topic: F.04. Voluntary Movements

Support: NIH
NINDS
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NCS
JASSO

Title: Utility-optimized RNN models produce reward-modulated movements and recapitulate known features of motor cortex activity

Authors: *S. EHRHARDT[1], H. MIYATA[1], S. M. CHASE[2];
[1]Dept. of Biomed. Engin., [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: If you tell your little brother that you will reward him for cleaning the dishes with a slice of cake, you might expect that the dishes will be cleaned faster than if you had offered him an apple as reward instead. To your little brother, the effort of cleaning the dishes vigorously is only worthwhile when a large reward is offered. In fact, reward expectation has been shown to modulate behavior, leading to more vigorous movements and higher success rates in behavioral tasks. It has been suggested that this effect can be explained by optimizing utility in economic models of motor control, in which the time-discounted reward of an action is balanced against the effort required to perform it. How does the motor system implement this tradeoff? Recurrent neural networks (RNNs) are a compelling approach to testing this proposition because they are observable; neural activity and how it is optimized can be tracked and causally linked to behavior. Despite this, the role utility plays in optimizing movement has yet to be explored in RNN models. Therefore, we propose an RNN model to simulate reaching, trained according to utility. We found that by incrementally training networks first to optimize target error, and then utility, they learned a robust solution to produce naturalistic, utility-optimized behavior. We assessed the realism of this model according to 4 criteria: 1. Natural behavior: Models produce naturalistic reaches that are smooth and efficient. 2. Reward modulation: The kinematics of these reaches, including reaction time, acquisition time, and peak speed, are modulated such that reaches for high rewards are more vigorous. 3. Neural mechanism: Models learn neural activity patterns that match key features observed in motor cortical populations. In particular, the subspaces used for movement planning and execution are orthogonal in the high-dimensional neural space, each using distinct dynamics. 4. Robustness: Models' behavior is consistent and changes smoothly with changes in hyperparameters. By satisfying these criteria, we established that RNNs can learn to move and change their movements depending on reward context as animals do and that utility-optimization may contribute to this effect. These results suggest that RNN models provide a valid substrate to explore the computational effect of reward on neural activity in the motor cortex, and how it drives changes in behavior.

Disclosures: S. Ehrhardt: None. **H. Miyata:** None. **S.M. Chase:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Program #/Poster #: PSTR099.04/Z11

Topic: F.04. Voluntary Movements

Support: PAPIIT IN204023
SECIHTI CF-2023-I-654

Title: Beyond facial movement: Decoding internal state and taste experience through deep learning

Authors: *D. VILLEDA ARIAS[1], E. SALAZAR[3,4,2], I. O. PEREZ-MARTINEZ[5];
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Abstract: Facial expressions in rodents have emerged as reliable indicators of internal states. However, the neural mechanisms that integrate gustatory stimuli with the homeostatic state to produce stereotyped motor patterns remain poorly understood. This study investigates how gustatory facial dynamics are shaped by internal state (satiated versus thirsty) and experience (novice versus expert) and further determines the role of the circuit connecting the anterior insular cortex (aIC) and the anterolateral motor cortex (ALM). Orofacial kinematics of head-fixed C57BL/6 mice were assessed using machine learning techniques, employing gradient-oriented histograms (GOGs) and tracking of sixteen key facial points with DeepLabCut. Facial responses to gustatory stimuli consisting of water, 20% sucrose, and 1 M denatonium were analyzed under different homeostatic states and levels of habituation. To assess causality, optogenetic inhibition of aIC-ALM flow was synchronized with sucrose administration. The results revealed that facial configuration depends on stimulus valency; similarity analysis (HOGs) confirmed that sucrose evokes a stereotyped movement with a significantly greater magnitude in response to the aversive stimulus denatonium (Kruskal-Wallis, $p < 0.01$), although without significant differences relative to water. Furthermore, in the presence of thirst, the aversive response to denatonium was markedly amplified, showing marked gaping (lower mouth, $Z > 26$), while the response to water focused its kinematics on the oral region, reducing the auricular movements observed during satiation ($Z > 24$). Experience in expert mice induced significant motor refinement in response to sucrose (condition × time interaction, $F(90,2520) = 1.367$, $p = 0.0136$). Exaggerated ear and lip movements were suppressed, optimizing the licking pattern (vertical tongue excursion, $p < 0.001$) and prolonging the pleasurable facial configuration. Finally, optogenetic inhibition of aIC terminals in the ALM reduced the motor area under the curve (AUC). In conclusion, facial expression in rodents acts as a dynamic motor map modulated by homeostatic state and experience. The aIC-ALM circuit participates in translating the hedonic and survival value of the stimulus into orofacial sequences.

Disclosures: D. Villeda Arias: None. **E. Salazar:** None. **I.O. Perez-Martinez:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

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Title: Population Neural Dynamics across Manual and Joystick Interceptions in Macaque Motor Cortex

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Abstract: Intercepting moving objects requires compensating for sensorimotor delays. Unlike reaching movement toward a stationary target, which couples sensory cues and motor goals, intercepting a target moving with varying velocities decouples target location from movement endpoint, thereby dissociating sensory inflows from motor outflows. However, manual interception alone cannot distinguish between state estimation for the visual target and effector. Joystick interception, where the monkey moves a cursor to intercept a moving target with a joystick, alters effector mapping while preserving predictive demands. Thus, comparing motor cortical dynamics in the two tasks might dissociate spatial from effector-specific predictions. In the present study, we trained a macaque on manual and joystick interception and recorded motor cortical activity with high-density Neuropixels probes. To date, we have analyzed 9 sessions, and utilized a Python package called Bombcell to select units from spike sorting results, which yielded a total of 872 single- and multi-units. Condition-averaged principal component analysis (PCA) and uniform manifold approximation and projection (UMAP) on resampled whole trials, movement-onset (MO) +/-0.5 s, and MO +/-0.2 s exhibited a clear separation of trajectories among target speed conditions. Decoding accuracy evaluated across eight target direction zones varied by method: population vector analysis (PVA) was weak (0.17±0.04), support vector regression (SVR) was moderate (0.49±0.15), and support vector classification (SVC) performed best (0.57±0.11). To explain the poor PVA performance, we averaged activity over time from target onset to touch target, MO to 0.2 s after MO, and 0.2 s before MO to MO. After applying PCA/UMAP, we found that neural states corresponding to different directions were not distributed along a ring-like structure. Applying a non-uniform discrete Fourier transform to the time-averaged firing rates computed over the time window from MO to 0.1 s after MO revealed dominant second-harmonic components, suggesting a bimodal rather than classical unimodal tuning. Our ongoing recording might provide a deep insight into the comparison between manual

and joystick neural dynamics to separate muscle-related from goal-related sensorimotor prediction.

Disclosures: Y. Wang: None. **B. Gong:** None. **R. Zheng:** None. **H. Cui:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.06/Z13

Topic: F.04. Voluntary Movements

Support: NRF Grant RS-2025-02263462

Title: Somatotopic organization of motor thalamocortical connectivity revealed by in vivo microstimulation-fMRI in macaque monkeys

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Abstract: Primary motor cortex (M1) carries an orderly body map, extensively studied using brain stimulation and neuroimaging. A parallel somatotopy has been found in the motor thalamus from microstimulation and recordings in monkeys, and from intraoperative stimulation mapping in humans. Classical tracing studies show that the ventral lateral nucleus (VL) is embedded in a closed cerebello-thalamo-cortical loop. Yet direct in vivo evidence that the thalamic motor map can drive the cortical motor map in register has been lacking. To address this, we stimulated the motor thalamus with a depth-advanceable microelectrode while recording whole-brain activity using MION-enhanced 7-tesla fMRI in three anesthetized rhesus macaques. We first validated the approach by stimulating the caudal ventral posterolateral nucleus (VPLc), a key thalamic relay to primary somatosensory cortex (S1). Electrical microstimulation (EM; 300 μA, biphasic cathode-leading pulses, 13-pulse trains at 130 Hz) strongly activated S1 (28% of the S1 ROI), confirming the canonical VPLc-to-S1 projection. We then targeted the motor thalamus in and around the VL by advancing the electrode ventromedially during fMRI. Based on reported somatotopy in VL (dorsolateral-to-ventromedial axis for foot-arm-face maps) and M1 (medial-to-lateral axis for foot-arm-face maps), we predicted that dorsolateral versus ventromedial VL stimulation would preferentially drive medial versus lateral M1, respectively. Consistent with this prediction, the centroid of the dominant M1 activation cluster shifted laterally as the stimulation site advanced ventromedially through the VL region (n = 2), suggesting somatotopically organized motor thalamus-to-M1 connectivity aligned with the cortical motor homunculus. Furthermore, EM co-activated additional nodes of the broader cortico-cerebellar circuit—the pontine nuclei, cerebellum, and red nucleus. Activation patterns across hemispheres respected dentato-rubral anatomy: dentate activation was confined to the hemisphere contralateral to the stimulated thalamus, whereas red nucleus activation was ipsilateral, with

dentate and red nucleus activity covarying. Finally, we explored higher-order thalamic nuclei such as the pulvinar and lateral posterior nucleus, whose stimulation evoked broad activations across the dorsal visual stream and posterior parietal cortex. Together, these results provide an in vivo, microstimulation-based functional map of thalamocortical and associated subcortical circuitry in the non-human primate brain, with implications for precision deep brain stimulation.

Disclosures: J. Lee: None. **M. Han:** None. **S. Kim:** None. **H. Sohn:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

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National Key R&D Program of China Grant 2017YFA0701102

Title: Neural mechanisms underlying interceptive reaching in intrinsic coordinates

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Abstract: Understanding how the brain interacts with dynamic environments is fundamental to systems neuroscience, yet much less is known. Recent studies have shown that motor cortical activity encoding upcoming movements is influenced by ongoing target motion during manual interception (Zhang et al. eLife 2025), and that preparatory activity in motor cortex shifts under force-field perturbations during a center-out task (Sun et al. Nature 2022). To disentangle the kinematic and kinetic components of mixed selectivity in motor cortical activity during predictive sensorimotor control, we trained a macaque to intercept a target that either moved along a circular path at a constant angular velocity (clockwise: -120°/s or -240°/s; counterclockwise: 120°/s or 240°/s), or remained stationary (0°/s) using a planar two-link manipulandum. The device constrains hand movement to the horizontal plane and restricts wrist motion, allowing endpoint trajectories to be mapped onto shoulder- and elbow-dependent joint kinematics. Endpoint speed profiles were bell-shaped across target conditions (16 sessions, 8225 trials), suggesting that interception was executed largely as a feedforward, ballistic movement rather than through continuous online correction. Trajectory analyses further suggested a consistent interception strategy for moving targets. Rather than approaching the target along a path approximately perpendicular to its motion, the monkey tended to overpredict the future target position and intercept it tangentially from the opposite direction of target motion. For example, when the target moved clockwise, the cursor often approached counterclockwise to meet the target. Clockwise and counterclockwise target conditions therefore produced a

convergent “hugging” pattern. These results suggest that manual interception engages internal execution strategies that differ across target dynamics and may be better understood in joint- and muscle-related coordinates. Our ongoing work will combine this behavioral framework with motor cortical recordings and force-field perturbations to examine how neuronal tuning and population dynamics relate to target motion, intended movement, joint-level execution variables, and dynamical adaptation.

Disclosures: S. Shu: None. **B. Gong:** None. **H. Cui:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

Support: R01NS104898
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U01DA063534

Title: Feedback-driven sensorimotor cortical dynamics during natural prey capture

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Abstract: How motor cortex controls movement during natural, continuously corrected behavior is largely unknown, because our understanding rests almost entirely on studies of trained, constrained reaching. We recorded sensorimotor cortex in two marmosets freely capturing live prey, a behavior that separates into ballistic quick captures and dynamic pursuits requiring corrections of the hand to account for evasion. During quick captures the population expressed canonical reaching signatures: near-orthogonal preparatory and movement subspaces despite no instructed delay, and strong rotational dynamics. Pursuit's more elaborate trajectories occupied the same low-dimensional geometry as quick capture. Within this geometry, corrective movements formed a distinct regime: preparation no longer led movement, trajectory tangling increased, and a slower, smaller rotation restarted from a non-canonical initial state. Nonetheless, a shared sequential firing-rate backbone underlay every movement type. Thus canonical reaching dynamics generalize to natural behavior and recast sensorimotor cortex as a controller that exploits autonomous dynamics under continuous feedback.

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Poster

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Title: Uncertainty engages the motor cortex during behavior

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Abstract: The motor cortex is a key component of the mammalian motor system, yet its importance for behavior can vary dramatically. It is essential for controlling movements in some contexts and largely dispensable in others, particularly in rodents. However, the factors that govern when and why the motor cortex is recruited to control movements as behavioral demands evolve remain poorly understood. Here, we use a combination of high-density neural recordings, optogenetic perturbations, and statistical modeling across multiple novel behavioral paradigms in the mouse to determine when and why the motor cortex is engaged in, and disengaged from, behavior. We demonstrate that motor cortical involvement in movement can toggle on and off through rapid, discrete state transitions, even during movements that otherwise appear continuous. Examining and manipulating behavioral triggers of state transitions revealed that motor cortical engagement is evoked under conditions of sensorimotor uncertainty and dissipates rapidly when sensorimotor contingencies are resolved and actions and outcomes become predictable. To determine whether and how the larger motor system reconfigures across motor cortical state transitions, we performed simultaneous recordings from the motor cortex and other motor regions - including the superior colliculus, thalamus, and basal ganglia. We find that motor cortical engagement and disengagement are accompanied by coordinated, large-scale changes in activity across the motor hierarchy, indicating that these transitions are not confined to the cortex but reflect a systems-level reorganization of motor control. Together, these findings provide a conceptual framework for when and why motor cortical control is engaged as behavioral demands evolve and how state transitions are coordinated across the broader motor system.

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Poster

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Topic: F.04. Voluntary Movements

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Title: Improved motor precision with multidimensional neural trajectories

Authors: W. LEE[1], X. SCHERSCHLIGT[2], M. NISHIMOTO[3], ***A. G. ROUSE**[4];
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Abstract: Neurons in motor cortex represent upcoming movement variables. If a neuron represents a movement variable, the most precise representation would likely occur when the neuron's firing rate directly matches the given variable. However, since the firing rates of individual neurons are noisy, precisely decoding movement from firing rates, such as in brain-computer interfaces, requires combining neural firing rates across a population.
When examining a neural population, it is typically assumed the most precise strategy would also have each neuron's firing rate match the movement variable. However, there is considerable evidence that neurons do not have synchronized firing rates that all similarly represent a movement variable. The dynamic firing rates of a neural population exhibit diverse timing relative to movement and varied patterns of coordinated activity. These differences in timing and co-activation lead to curved neural trajectories through the neural space rather than a single neural dimension matching a movement variable.
Here, we examined how these curved neural trajectories might influence the precise representation of a movement variable. Based on analysis of neural data from primary motor cortex during a task with multiple reach distances, we built a simulated neural population which varied its representation of movement velocity with two additional strategies: Timing Variation and Selective Co-activation. In Timing Variation, each neuron increased its firing rate at different times relative to the onset of movement. In Selective Co-activation, different combinations of neurons were active for small versus large velocity movements. We then employed a recurrent neural network which integrated a Multilayer Perceptron (MLP) and a Long Short-Term Memory (LSTM) network to train on the hypothesized encoding models and to evaluate decoding performance from these models.
The decoding accuracy for the simulated neural representations were compared to a Linear model where all neurons were synchronized and directly matched movement velocity. Our results show that these two simple strategies—Timing Variation and Selective Co-activation—were used by the recurrent neural network to infer more information about the desired movement and improve motor precision. These results demonstrate these two widely observed neuronal

features are sufficient to generate population trajectories that improve motor precision and are robust to noise. Finally, a combined strategy was an even more accurate representation. These properties have direct implications for the robustness and reliable control of neural decoding and brain-computer interfaces.

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Poster

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Topic: F.04. Voluntary Movements

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Title: Quantitative mapping of the laminar and regional structural connectivity of the dorsal-rostral (6DR) premotor cortex in the macaque monkey brain

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Abstract: The dorsal-rostral premotor (6DR) cortex is a cortical region involved in higher-order motor functions that depend on its interconnections with other motor-related cortices and higher-order prefrontal areas. Projections from 6DR target distinct cortical layers in different regions, which can influence information flow within premotor areas. However, while the laminar origin of premotor connections has been studied with retrograde methods, the quantitative laminar termination patterns of 6DR projections measured with bouton and axon density remain largely uncharacterized in primates. This study uses tracer injections in 6DR of rhesus monkeys (n = 4, both sexes, aged 5-7 yrs) to quantify laminar axons and terminations (boutons) in medial (6M, 6Ms, 24C), ventral (6VC, 6VR and 44), and dorsal-caudal (6DC) premotor areas using unbiased stereological analysis. Bouton density from 6DR injections was highest in area 6DC, intermediate in areas 44, 6M, 6Ms, 24C, 6VC, and lowest in area 6VR. Laminar analysis showed that 6DR boutons were distributed in a columnar pattern across superficial and deep layers in target areas. This analysis was supplemented by exhaustive manual tracing of axons in target regions. Axon density was highest in areas 6DC and 44, intermediate in areas 6M, 6VR, 6VC, and lowest in areas 24C and 6Ms. Laminar analysis showed that axon density did not exhibit consistent differences across layers or areas. Evaluation of bouton density and inter-bouton intervals in individual axons identified regions consistent with focal or dispersed termination patterns. Comparison of axon density and bouton density within the same case showed that bouton density was higher than axon density for dorsal and medial premotor areas, but axon density was higher than bouton density for rostral and ventral premotor areas. Overall, these data

show that 6DR projects to other premotor areas with varying density of axonal boutons and fibers, and that these estimates of connectivity may vary according to area.

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Poster

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Topic: F.04. Voluntary Movements

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Pennsylvania HRFG

Title: A spiking neural network model of state transitions in the motor cortex during reaching

Authors: *H. MAO[1], B. HASSE[1], A. SCHWARTZ[2];
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Abstract: Single-unit firing rates in the motor cortex can be multiphasic during straight arm reaches, suggesting transitions of neural state during single movements. However, what drives such neural state transitions is not well understood. Here, using a spiking neural network model with putative dynamic inputs, we studied the structure of synaptic integration that could give rise to the observed motor cortical neuronal activity.
Two rhesus monkeys performed a center-out reaching task while neural activity was recorded from M1 and PMd using Utah arrays. Using LFADS, single-trial neural activity was generated by an autonomous model whose initial state was inferred from recorded activity in a data window. We predicted firing rates from different models to decode reaching velocity, and models with an initial state inferred from pre-movement neural activity produced substantially larger decoding errors compared to those initialized using activity after movement began. Therefore, the state transitions during reaching are unlikely to be generated from a pre-movement template in the absence of ongoing extrinsic inputs.
Our previous analysis revealed three 2-D neural activity planes, each representing a unique neural state. Projections of single-trial neural population activity onto these planes had monophasic temporal peaks that matched the timing of one of three behavioral events: movement onset, peak speed and movement offset, respectively. Accordingly, we assume that neural states in the motor cortex are associated with ongoing, behavior-linked extrinsic inputs. Feedforward spiking neural networks (SNN) were trained to reconstruct the observed state transitions using three putative groups of dynamic input. Each group was associated with one of the behavioral events. A fourth group was generated to represent the non-directional component of recorded neuronal activity. The SNN output units corresponded to recorded motor cortical neurons and were fully connected with all input units. Synaptic weights were learned from input

and output spike trains following the Hebbian rule. The resulting firing rates of the output neurons matched those of motor cortical neurons reasonably well. Further analysis focused on how action potentials of output units were generated through synaptic integration. Our SNN modeling shows that a range of tuned input units with preferred directions near the movement direction fire at a high rate and contribute to the buildup of an output neuron's membrane potential toward threshold, while those with the largest weights (tuning matching that of the output neuron) are most likely to trigger the spike, even when firing at a low rate.

Disclosures: H. Mao: None. **B. Hasse:** None. **A. Schwartz:** None.

Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

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Title: Mapping Lateral Rostral Medulla Activation and Functional Connectivity Using Optogenetic fMRI

Authors: V. JINDAL[1], M. M. GRUDNY[2], *S. VAHDAT[3];
[1]McLean Hosp., Belmont, MA; [2]Psychiatry, Univ. of Florida, Gainesville, FL; [3]Univ. of California Riverside, Riverside, CA

Abstract: Introduction: The lateral rostral medulla (Lat-RM) is increasingly recognized as a brainstem central hub for the execution of skilled forelimb movements, receiving organized cortical and striatal inputs and sending descending projections to the caudal medulla and cervical spinal cord. Yet the organization of its projections to cortical and subcortical targets remains incompletely characterized. Here, we combined optogenetic stimulation with functional magnetic resonance imaging (opto-fMRI) to map downstream activation patterns and functional connectivity associated with glutamatergic neurons in the Lat-RM. Methods: Adult male Vglut2-Cre mice received unilateral injections of a Cre-dependent AAV1-double floxed-ChR2-EYFP vector and optical fiber implantation targeting the right Lat-RM. Four weeks later, after validation of viral expression and optical fiber targeting by evoked muscle twitches in the right forelimb, mice underwent opto-fMRI under anesthesia. Lat-RM was stimulated using 10 Hz blue light (473 nm, 1 mW) in a block-design paradigm. We mapped brain-wide activation and functional connectivity associated with Lat-RM stimulation and examined their statistical dependence on thalamic activity. Results: Optogenetic stimulation of Lat-RM glutamatergic neurons produced widespread bilateral activation across sensorimotor, cingulate, retrosplenial, and insular cortices, as well as the thalamus, basal ganglia, hippocampus, cerebellum, and multiple medullary nuclei. Although activation was generally bilateral, cerebellar and brainstem responses were stronger ipsilaterally. Functional connectivity analyses revealed lateralized

interactions between the Lat-RM and distributed motor networks spanning cortical, subcortical, cerebellar, and brainstem structures. Regressing out thalamic activity significantly reduced activation across cortical and basal ganglia regions, suggesting that Lat-RM influences forebrain circuits through polysynaptic thalamic pathways. Conclusions: The distributed downstream cortical and subcortical networks linked to LatRM glutamatergic stimulation suggest that the Lat-RM engages coordinated brain-wide motor circuits via feedback loops rather than acting solely as a downstream motor relay. Attenuation of forebrain activation following thalamic regression supports a thalamic relay linking brainstem and forebrain circuits. Together, these findings support a polysynaptic cortico-medullary-cortical network involved in forelimb motor control.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Title: Title: Motor Preparation and Reward Shape Cortical Traveling Wave Motifs

Authors: *D. AAKER[1], O. KOLHE[1], H. KHAN[1], K. JAYANT[1,2];
[1]Biomed. Engin., Purdue Univ., West Lafayette, IN; [2]Purdue Inst. for Integrative Neurosci., West Lafayette, IN

Abstract: Title: Motor Preparation and Reward Shape Cortical Traveling Wave MotifsAuthors: Dalton Aaker[1], Om Kolhe[1], Hammad Khan[1], Krishna Jayant[1,2]**Affiliation:** [1]Purdue University, Weldon School of Biomedical Engineering, West Lafayette, IN, USA[2]Purdue Institute for Integrative Neuroscience, West Lafayette, IN, US**Abstract:**Cortical traveling waves propagate across the neocortex during diverse cognitive and motor operations, yet how distinct propagation motifs, planar versus rotational, map onto specific computational demands remains poorly understood. Recording surface local field potentials and single-unit spiking activity from the primary motor cortex of mice using custom fabricated NeuroGrids, we find that propagating wave geometry is systematically shaped by task context: planar wavefronts are modulated by reward delivery, while rotational dynamics emerge selectively during motor preparation and execution. Rotationality is consistently strongest in the period immediately preceding movement initiation for both cued and spontaneous movements, suggesting a predictive role in motor planning. Neural subspace analysis of spiking dynamics reveal that wave-carrying and movement-encoding neurons substantially overlap, indicating that distinct

propagation patterns reflect the differential recruitment of shared, task-relevant circuits rather than segregated wave-generating populations. These findings reframe cortical traveling waves not as epiphenomenal byproducts of motor activity, but as structured geometric signatures of the underlying computational state.**Funding**: This work was supported by the following grants to K.J.: the Air Force Office of Scientific Research under award numbers FA9550-23-1-0701 and FA9550-26-1-0004 - AFOSR (MURI). Any opinions, findings, conclusions, or recommendations expressed in this material are those of the author(s) and do not necessarily reflect the views of the United States Air Force. This work was also supported by the National Institutes of Health New Innovator Award (DP2MH136494).

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Poster

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Topic: F.04. Voluntary Movements

Support: NIH R01 grant number NS111148

Title: Direction-Invariant Encoding of Arm Stiffness in Motor Cortex

Authors: *B. HASSE[1], H. MAO[1], F. TESSARI[3], N. HOGAN[3], A. SCHWARTZ[2];
[2]Neurobio., [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]MIT, Cambridge, MA.

Abstract: During voluntary reaching, the nervous system must simultaneously control movement direction and arm impedance. Whether these properties are encoded independently in motor cortex, or whether stiffness representations are entangled with directional tuning, remains unclear. We investigated this using a ballistic-release task in which a non-human primate pre-set arm stiffness across eight movement directions and nine stiffness conditions (3 force × 3 displacement levels) prior to movement onset. Neural activity was recorded from primary motor cortex via 2 Utah arrays.

Individual linear decoders were trained within each movement direction to predict arm stiffness from population activity, stiffness ~ $a_{1\text{-}N}$*$FR_{1\text{-}N}$ + b (a: coefficients, FR: firing rates, b: bias, N: # neurons); R^2 scores ranged from 0.42 to 0.77. The model performed poorly when trained across all directions (R^2 = -0.12) but improved substantially after removing the mean firing rate for each direction (direction-adjusted R^2 = 0.37), confirming that stiffness signals are partially obscured by the dominant directional drive. Backwards elimination of regressors identified movement direction as the primary predictor of firing rates. Though smaller, force, displacement, stiffness, damping, and mass each accounted for a significant amount of the neural variance with roughly equal contributions.

To test whether stiffness encoding is stable across movement directions, we fit each neuron's firing rate using force and displacement within each direction. These stiffness tuning profiles

were compared across movement directions using cosine similarity in a leave-one-direction-out cross-validation framework. Stiffness tuning was highly consistent across directions (mean cosine similarity = 0.57 for significantly tuned neurons, 0.39 across all neurons; both $p < 10^{-120}$ vs. shuffled control). A Rayleigh test confirmed non-uniform clustering of preferred stiffness tuning angles ($p \approx 0$), indicating neurons encode stiffness along a consistent axis in force-displacement space regardless of movement direction.
The complementary analysis tested whether directional tuning is stable across stiffness conditions. Using a leave-one-stiffness-condition-out procedure, directional tuning consistency was near-ceiling (mean cosine similarity = 0.89; $p \approx 0$), indicating preferred directions are essentially unchanged by stiffness demands. These results demonstrate that stiffness and directional encoding are substantially independent in motor cortex, supporting a model in which impedance control is a separable, direction-invariant computation within the motor cortical population.

Disclosures: B. Hasse: None. **H. Mao:** None. **A. Schwartz:** None.

Poster

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Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS125435

Title: Combined Reward-Effort Context Reveals Reward-Dependent Modulation of Sensorimotor Granger Causality Before Movement Planning

Authors: *A. PRAKASH[1], T. YADAV[2], J. T. FRANCIS[1];
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Abstract: Reward and effort are known to influence behavior and neural activity. However, it is unclear how expected reward and effort modulate communication within sensorimotor circuits before motor planning. To address this gap, local field potentials (LFPs) were recorded using 96 electrodes implanted across the Primary Motor Cortex (M1), Primary Somatosensory Cortex (S1) and Dorsal premotor cortex (PMd) of a macaque performing three cued center-out reaching paradigms. Visual cues indicated reward level, effort level, or both before target onset, dissociating affective context from motor planning. We tested whether cue context modulated band-limited Granger Causality (GC) across directed sensorimotor pathways in alpha (8-13Hz), beta (14-30Hz), low-gamma (30-80Hz), and high-gamma (80-200 Hz) frequency bands. Trial-wise spectral GC was computed using a state-space approach and averaged within each band. GC was analyzed across six directed pathways: M1->PMd, M1->S1, PMd->M1, PMd->S1, S1->M1, and S1->PMd. Cue-level modulation was tested using Kruskal-Wallis tests, followed by pairwise rank-sum post hoc tests with false-discovery-rate correction. Reward-only trials were

compared across R1/R2/R3, effort-only trials across E0/E1/E2/E3. Reward-effort trials were analyzed by either varying effort at fixed reward or varying reward at fixed effort. To assess directionality, the original GC and the time-reversed GC were compared, and bootstrap was used to assess stability. Time-reversal directed asymmetry revealed directed GC structure across tasks. M1->S1 showed directed structure across all bands in the reward-effort task. Cue-level modulation was more selective. For the reward-only task, no significant differences were observed for the Kruskal-Wallis test. However, in the reward-effort task, significant differences were observed when reward was varied at fixed effort. This modulation was most evident in the M1->S1 pathway, where the beta band showed significant R1 vs R3 differences across multiple fixed effort levels, while the low-gamma band showed R1 vs R3 differences for all effort levels. Effort-related modulation was weaker. Effort-only beta and high-gamma GC passed the Kruskal-Wallis test for PMd->M1 and M1->PMd pathways respectively, but did not survive post hoc correction. Similarly, varying effort at fixed reward did not survive post hoc correction. These results suggest that combined reward-effort context may reveal reward-dependent modulation of M1->S1 communication before movement planning, suggesting a mechanism by which motivational value influences upcoming action.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR099.17/Z24

Topic: F.04. Voluntary Movements

Support: NYS DOH1-C32250GG-3450000
NIBIB U24EB028998

Title: Motor cortex multiscale mechanistic model tuned to reproduce spike-based neural manifolds during forelimb push/pull movements

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Abstract: Primary motor cortex (M1) generates descending commands for skilled forelimb movements. Low-dimensional neural manifolds extracted from population activity have proven powerful tools for decoding and predicting behavior across species and tasks, yet the circuit-level mechanisms that give rise to these manifolds remain unclear. We previously developed a multiscale mechanistic model of mouse M1 that reproduces experimentally recorded spiking, local field potentials, and condition-dependent population dynamics. Here, we extend this

framework using Neuropixels spike-time recordings from the caudal forelimb area of mice performing a cued push/pull lever task. This dataset provides trial-resolved spike times aligned to cue onset or movement initiation, together with reaction times, movement durations, unit depths, and spike-width information, enabling spike-based analysis of motor cortical dynamics across successful and missed push and pull trials.
We will use CEBRA to learn behavior-conditioned latent embeddings from binned spike trains, trial type, movement direction, cue timing, movement onset, and movement duration. These experimentally derived manifolds will be used as optimization targets for a biologically detailed NetPyNE/NEURON model of M1 containing layer-specific excitatory and inhibitory populations, long-range inputs, and corticospinal output neurons. Model calibration will test which circuit mechanisms best reproduce the observed spike-based neural manifolds, including changes in long-range input timing and strength, local recurrent connectivity, excitation/inhibition balance, and layer- or cell-class-specific synaptic organization. Unit depth and spike-width metadata will be used to constrain comparisons between simulated neuronal populations and recorded regular-spiking or fast-spiking units.We will evaluate whether the model reproduces key experimental features of our collaborators' dataset: dominant movement-invariant dynamics around movement initiation, sparse movement-specific encoding of push versus pull actions, and differences in population structure across behavioral conditions. By linking spike-based latent manifolds to identified model cell classes, synaptic connectivity, and biophysical mechanisms, this work provides a mechanistic bridge between experimentally recorded motor cortical population dynamics and the descending cortical activity patterns that shape skilled forelimb movement.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Program #/Poster #: PSTR099.18/AA1

Topic: F.04. Voluntary Movements

Support: R01 NINDS R35 NS122333
R01 NINDS R01 NS125270

Title: Neural correlates of joint torques during primate prehension

Authors: *A. R. SOBINOV[1], X. MA[3], N. CARR[5], E. OKOROKOVA[6], S. J. BENSMAIA[2], N. G. HATSOPOULOS[1], L. E. MILLER[4];
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Abstract: A hallmark of primate behavior is the exceptional ability to grasp and manipulate objects dexterously, but the investigation of the neural mechanisms that support manual dexterity has been challenging. Contact forces are hard to measure with sufficient spatial and magnitude precision, and joint torques, which could provide a continuous mechanical description across both reaching and object manipulation, are almost impossible to measure directly. Estimating these torques in the complex primate hand could therefore provide an important means to understand the neural activity underlying manual dexterity.
With this in mind, we have developed an experimental apparatus and data processing pipeline for quantifying torque, joint angles, and contact forces during prehension. The apparatus presents objects of various sizes and orientations throughout the peripersonal space, thereby evoking different grasping strategies. Object surfaces were instrumented with thousands of pressure-sensitive elements to measure distributed contact forces, while eight high-speed cameras tracked hand and arm movements. Using the tracked movements, reconstructed contact forces and a musculoskeletal model of the hand, we computed inverse dynamics, yielding joint torques throughout behavior. With this system, we examined the activity of individual motor cortical neurons in relation to grasp force, kinematics, and torques, providing an initial basis for testing how joint torques are reflected in neural activity. Together, this framework enabled a comprehensive and precise physical characterization of primate manual behavior, providing a foundation for further investigation of the neural mechanisms of manual dexterity.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

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Program #/Poster #: PSTR099.19/AA2

Topic: F.04. Voluntary Movements

Support: Lundbeck Foundation R483-2024-1882

Title: Spinal cord population activity lacks rotational dynamics during an alternating isometric task in macaques

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Abstract: Motor cortex neural activity exhibits rotational population dynamics during reaching, and recent recordings from turtle, cat, and mouse lumbar spinal cord suggest rotational structure may be a general feature of spinal cord circuit activity, contrary to a large body of spinal cord literature. However, those studies examined rhythmic multi-joint behaviors (locomotion, scratching), in which sequential activation across joints can produce apparent rotation independently of the underlying computation. We tested whether spinal cord neuronal activity exhibits rotational dynamics during non-rhythmic, single-joint isometric contractions. We re-analyzed neuronal recordings from three rhesus macaques performing an alternating isometric wrist flexion/extension torque task (step-ramp-hold, visual feedback). Cervical spinal interneurons (C6-T1, ipsilateral) were recorded in two monkeys; primary motor cortex units (hand area, contralateral) was recorded in a third as a positive control, using identical hardware, spike-sorting, and analysis. Forearm EMG was recorded in all animals. PCA was applied to task-modulated units (n=379 spinal across two monkeys, n=334 cortical, n=47 corticomotoneuronal [CM] cells), and trajectory geometry was quantified by an anisotropy ratio (PC1/PC2 variance).Individual spinal interneuronal activity showed robust directional tuning. At the population level, cortical variance was distributed roughly equally across PC1 and PC2 (anisotropy ≈1.4), producing near-circular, rotational trajectories and replicating prior cortical findings. In spinal cord, variance was captured almost entirely by PC1 (anisotropy 2.3-3.3), yielding elongated, one-dimensional trajectories that reflect alternating rather than rotational dynamics; EMG showed the same collapsed geometry (anisotropy ≈4.9). Activity of CM cells had distributed variance across PC1 and PC2 like activity of other cortical units rather than that of spinal populations or muscles, despite their direct synaptic linkage to motoneurons.These results indicate that rotational dynamics are not preserved across the cortico-spinal axis during single-joint tasks. Spinal population activity instead reflects rapid switching between antagonist-related states, consistent with a direct transformation of descending commands into muscle activation. Task structure, rather than rotational computation per se, likely accounts for previously reported spinal rotations during rhythmic movement.

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Poster

PSTR099: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

Support: NIH T32

Title: Constraining inference of across-region interactions using neural activity perturbations

Authors: *D. BASRAI[1], A. KRISTL[2], P. WANG[3], A. MIRI[4], J. I. GLASER[1];
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Abstract: Understanding neural system function requires characterizing functional interactions within networks of neurons across the brain. Models are commonly trained to infer these interactions by learning connection strengths that best predict naturally occurring neural activity patterns recorded in behaving animals. While this approach is increasingly applied to quantify interactions between brain regions from multi-region recordings, the space of well-fitting model parameters may be quite large, which would render across-region interactions ambiguous. Instead of fitting models solely to naturally occurring neural activity, theoretical results suggest models can be better constrained by fitting to activity patterns that include the effects of activity perturbations. We therefore examined how well multi-region recordings alone constrain estimates of across-region interactions, and whether including region-wide perturbations better constrains these estimates.

To do so, we simultaneously recorded neural activity in two connected regions (primary and secondary forelimb motor cortex) and sporadically silenced activity in one region optogenetically while mice performed a naturalistic climbing task. We trained models to predict activity in each region from preceding activity in both regions. When trained solely on naturally occurring neural activity, models spanning a broad range of across-region interaction strengths fit the observed data nearly equally well. In contrast, models trained on activity that included optogenetic perturbations identified a narrow range of well-fitting estimates of across-region interactions. Model weights learned from activity that included perturbations differed substantially than those learned from natural activity alone, demonstrating that perturbations non-trivially alter estimates of connectivity.

To examine whether these constrained estimates reflect the actual functional connectivity of the system, we inferred connectivity from simulations generated from a multi-region recurrent neural network (RNN). Models fit to simulated activity that included region-wide perturbations produced constrained estimates of across-region interactions that closely matched the RNN's actual connectivity. Furthermore, models trained solely on natural activity inferred strong, excitatory across-region weights from neurons that did not make across-region connections. Together, these results indicate that the inclusion of region-wide activity perturbations enables precise and accurate estimates of across-region interactions that cannot be inferred from naturally occurring activity alone.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

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Topic: F.05. Brain-Machine Interface

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Title: Adaptive Neural Reorganization Enables Real-Time Finger-Level Robotic Control in BCI-Naïve Stroke Survivors

Authors: *Y. DING[1], M. KARRENBACH[2], Z. JOHNSON[1], H. WANG[1], J. ZHANG[1], G. F. WITTENBERG[3], B. HE[1];
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Abstract: Restoring dexterous hand function remains a major challenge following stroke, particularly for tasks requiring individuated finger control. Noninvasive brain-computer interfaces (BCIs) offer a promising approach by translating neural activity into control signals for assistive devices (Edelman et al., 2024). However, most prior work has focused on low-dimensional or limb-level outputs. Whether fine finger-level control can be achieved in BCI-naïve stroke populations using electroencephalography (EEG) remains unclear (Ding et al., 2025).
A cohort of nine stroke-affected participants with no prior BCI experience performed real-time BCI tasks to control a robotic hand through imagined finger movements decoded from EEG. Participants controlled the robotic hand using their affected hand when applicable, or their dominant hand otherwise.
Participants achieved average decoding accuracies of 84% for two-finger tasks (thumb vs. pinky) and 61% for three-finger tasks (thumb vs. index vs. pinky), demonstrating reliable finger-level control. Notably, decoding performance improved following inclusion of low-frequency EEG components (0.5-4 Hz). In an additional session with randomized interleaving of bandpass conditions (0.5-40 Hz vs. 4-40 Hz), a linear mixed-effects model revealed a significant main effect of bandpass ($z = 2.124$, $p = 0.034$).
Comparisons of task-elicited neural responses between stroke survivors and healthy participants revealed clear alterations in the oscillatory patterns of task-induced cortical dynamics. Specifically, stroke survivors exhibited a more bilateral pattern of event-related desynchronization with unilateral movement intention, accompanied by a reduced amplitude. In addition, motor-related cortical potential responses were attenuated and delayed relative to healthy controls. Electrophysiological analyses also revealed globally reduced alpha-band functional connectivity alongside enhanced delta-band connectivity particularly in the contralesional hemisphere. Consistently, the delta-alpha ratio was elevated in stroke participants. These findings demonstrate the feasibility of noninvasive, finger-level BCI control in BCI-naïve stroke survivors. The electrophysiological findings are consistent with the literature regarding the neural reorganization after stroke. Our findings also suggest that motor-related information in stroke is increasingly encoded within slower oscillatory dynamics. These results provide electrophysiological evidence that the observed shift in decoding contributions from alpha to delta bands reflects an underlying reorganization of neural dynamics.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

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Program #/Poster #: PSTR100.02/AA5

Topic: F.05. Brain-Machine Interface

Support: DP5OD029571
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Myomo Inc

Title: Routine and Sustained Home Use of an Assistive Myoelectric Orthosis: A Pilot Study in Chronic Stroke

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Abstract: Upper-limb myoelectric orthoses can improve the functional ability of stroke survivors with limited arm function due to chronic hemiparesis. Although widely used to support activities of daily living, little research has investigated how these devices are used in everyday life. In this study, we logged motor activations from a hand and elbow myoelectric orthosis with four stroke survivors with chronic hemiparesis. The stroke survivors used the Myomo MyoPro® myoelectric orthosis during in-clinic therapy and at-home activities for approximately three months. Data logs demonstrated sustained daily use of the device. Participants' unsupervised home use was significantly greater than supervised in-clinic use ($p < .005$, ANOVA). Participants engaged the assistive hand functions more than the assistive elbow functions ($p < .005$, ANOVA), as they activated the hand an average of 787.8 times per week and the elbow an average of 283.4 times per week. The number of motor activations per minute the device use in-clinic (6.35 ± 2.78) versus at-home (5.59 ± 3.2) was statistically indistinguishable ($p = .063$, ANOVA), indicating that participants used the device at home with a similar intensity to that in the clinic. Across all participants, a given therapy session was associated with an average of 221 hand activations and 114 elbow activations; by these numbers, we estimate the rehabilitative effect of home use to be equivalent to approximately 2-4 additional therapy sessions per week. This work provides some of the first quantitative evidence that stroke survivors demonstrate sustained at-home use of prescribed myoelectric orthoses, a key finding that is likely to support reimbursement. More broadly, this work demonstrates that quantitative data from assistive devices can provide valuable insight into patient and therapist activities, which may ultimately improve motivation, adherence, and outcomes.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.03/AA6

Topic: F.05. Brain-Machine Interface

Support: Department of Mechanical Engineering, Carnegie Mellon University
Neuroscience Institute, Carnegie Mellon University

Title: A shared dynamics representation for prediction- and control-relevant computations

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Abstract: Skilled movement requires the nervous system to act before delayed sensory feedback can fully correct errors. This has motivated the idea that the brain uses internal models to estimate the consequences of motor commands and to generate the forces needed for intended motion. At the mechanical level, these functions depend on two coupled dynamics problems: inverse dynamics, which maps motion to the forces or torques required to produce it, and forward dynamics, which maps applied forces or torques to the resulting motion. Although these problems are constrained by the same body mechanics, they are typically treated as separate mappings. This separation leaves unresolved whether prediction- and control-relevant dynamics could be supported by a common representation. Here, we test this possibility by introducing an Appellian Neural Network (ANNet) grounded in the Gibbs-Appell formulation of analytical mechanics. ANNet maps joint position, velocity, and candidate acceleration to a single scalar quantity: Appell acceleration energy. Inverse dynamics is obtained by differentiating this learned scalar with respect to acceleration to recover joint torques. Forward dynamics is then solved without training a separate forward model by embedding the same learned energy landscape in an optimization objective whose minimum satisfies the Gibbs-Appell equations. We evaluated ANNet in a simulated two-link pendulum, a minimal model of coupled limb dynamics. A four-hidden-layer network with GELU activations was selected by hyperparameter search and trained using derivative-based torque supervision. Inverse-dynamics accuracy improved with training-set size and reached an efficient operating point at 16,000 samples, with median torque RMSE of 0.0242 Nm and 0.0234 Nm across the two joints. The same trained network supported closed-loop forward-dynamics simulation across 50 independent 5-s trajectories, with median angular

RMSE of 0.00737 rad and 0.0119 rad and mean update time of 1.62 ms. These results show that a single learned scalar energy landscape can encode the mechanical structure needed to solve both forward and inverse dynamics. This provides a first-principles computational framework for studying how the dynamics underlying prediction and control may be represented in a shared neural architecture.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

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Topic: F.05. Brain-Machine Interface

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Title: Real-time BCI control of a virtual third arm

Authors: *G. SCHRIFT[1], D. ABELES[2], O. DEZACHYO[1], N. CENSOR[2,1];
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Abstract: Motor augmentation aims to expand human action capabilities beyond biological anatomy by controlling supernumerary body parts. Augmented reality (AR) frameworks provide controlled yet ecologically valid conditions, however, a central challenge remains achieving reliable control of an additional effector and understanding its underlying neural mechanisms. Here we present an AR-based brain-computer interface (BCI) framework, enabling real-time control of a virtual third arm using electroencephalography (EEG)-based motor imagery (MI). Participants (N=7) wore a head-mounted display and experienced a spatially registered virtual third arm extending from their mid-torso. A haptic vest provided tactile feedback to promote embodiment. Following a familiarization phase, participants completed four classes of trials: Right hand MI, Left hand MI, Third hand MI, and fixed eye-gaze control (Idle state) trials. Data generated in these trials were subsequently used to train a classifier that controlled the third hand. EEG signals were recorded with a wireless system and processed through a pipeline including spatial filtering, Riemannian tangent-space projection, and linear discriminant analysis. Offline classification reliably distinguished the three MI states and the control Idle state from each other, achieving mean accuracy of 66%±7% standard error (chance=25%). Next, participants were required to use the BCI for real-time object manipulation. A classifier trained on Third hand MI vs Idle state using 2-second sliding windows with 250-millisecond steps resulted in mean accuracy of 76%±3% standard error. Using the third hand concurrently with their natural hands, participants successfully grasped, held and transported an object to a designated location before releasing it. Post-session questionnaires showed high levels of ownership, agency, and

engagement with the virtual hand. Time-frequency analysis revealed that Third hand MI elicited distinct Mu (8-13 Hz) and Beta (13-30 Hz) band event-related desynchronization (ERD). While natural hand MI produced classic contralateral ERDs, Third hand MI yielded a central sensorimotor pattern accompanied by bilateral posterior ERDs. Together, these results demonstrate that BCI control of a supernumerary limb is feasible after a single training session, and can support real-time, embodied interaction. The novel and unique Third hand ERD patterns suggest that the brain rapidly adopts distinct sensorimotor strategies for the extra effector. This paradigm provides a platform for studying the neural basis of motor augmentation and developing future rehabilitative technologies.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

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Title: Selective intrafascicular facial nerve stimulation for programmable facial movements and triggered eyelid closure in rats

Authors: *Q. LU[1], Z. ZHAO[2], X. LI[2];
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Abstract: Facial palsy disrupts volitional and synchronized facial movement, including protective eyelid closure, yet current reanimation strategies provide limited selective or programmable control of individual facial motor outputs. We investigated whether a transverse intrafascicular multichannel electrode implanted in the rat facial nerve trunk can provide selective, model-based control of facial movements and drive on-demand synchronized eyelid closure in a nerve-injury model. In 5 rats, multichannel electrodes were implanted in the facial nerve trunk, and stimulation was delivered across contacts while multi-effector responses (eyelid, whisker pad, nasal, and ear) were quantified by video-based kinematics. We constructed contact-by-effector recruitment maps, quantified stimulation selectivity, and fit a dose-response model incorporating multi-contact interaction terms, optimizing stimulation with a cost function penalizing target error, off-target activation, and injected charge. To address synchronized

closure after denervation, we used a facial nerve injury-suture-redirection model in which a vibrissal branch was coapted to drive orbicularis oculi, and tested contralateral-blink-triggered closed-loop stimulation in awake animals. Individual contacts selectively recruited distinct facial effectors, and the model reproduced multi-effector responses on held-out stimulation conditions, generating graded composite movements at low injected charge. Following reinnervation, stimulation of the redirected pathway shifted from predominantly evoking whisker movement to predominantly evoking eyelid closure. Closed-loop stimulation triggered by contralateral blink elicited time-locked eyelid closure at short latency in awake animals, and remained functional across repeated testing over weeks of chronic implantation. These results demonstrate that an intrafascicular facial nerve interface enables selective, predictive, and programmable control of composite facial movements and supports on-demand synchronized eyelid closure in a nerve-injury model, providing a foundation for closed-loop facial reanimation neuroprostheses.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

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Program #/Poster #: PSTR100.06/AA9

Topic: F.05. Brain-Machine Interface

Title: Discretize to Optimize: Improving End-Effector Velocity Control of Robotic Arms in BCIs

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Abstract: Brain-Computer Interface (BCI) control of robotic arms is a promising avenue for restoring independence to people with paralysis. Yet, precise and reliable control remains challenging due to the difficulty of accurately decoding a user's intended velocity into a robot's many degrees of freedom (DOF). The standard approach for BCI robot control translates neural activity via linear regression into continuous velocity commands, requiring users to control multiple DOFs at once. This work proposes a new decoding approach that represents the robot's six DOFs as 12 cardinal velocity directions (positive and negative motion along each axis), enabling single-velocity control at a time. This method employs Discrete Direction Selection (DDS), a multinomial logistic regression model for 6-DOF robot end-effector velocity control. DDS demonstrated strong performance in a prior BCI cursor-control study and has since been adapted for robot control. We hypothesize that discrete velocity control is advantageous over continuous decoding because it enables users to generate fewer neural inputs without compromising accuracy or task performance. Additionally, unlike traditional decoding methods for robot BCI control, DDS forgoes reliance on guided enhancements (e.g., shared control or target assistance) for optimized user performance. This work establishes a statistically rigorous

comparison between DDS and state-of-the-art continuous linear regression decoders for robot control. Such comparisons require a large subject pool, which is not feasible with an iBCI. Therefore, this study used a validated model (joint-angle BCI), in which hand kinematics from able-bodied users were processed by a neural emulator to generate simulated neural firing rates. Performance of both decoding models was evaluated using a timed 3D center-out task requiring users to pick and place objects at various locations and orientations within a fixed workspace. Pilot data were collected (n = 4) in a within-subjects study. Performance metrics included mean success rate and mean overall task score, with 1 point awarded for each completed task component (touch, grasp, lift, and place). Discrete control resulted in a higher mean success rate (47%) than continuous control (23%). The mean overall task score was also higher under DDS (100.75) than under continuous control (72.5). Preliminary results suggest the promise of discrete control as a new approach for optimizing robot-BCI user performance.

Disclosures: C.K.P. Nkwocha: None. **Z.C. Danziger:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.07/AA10

Topic: F.05. Brain-Machine Interface

Support: TRIF Fund, University of Arizona

Title: Wireless injectable muscle stimulators to restore movement in the paralyzed hand

Authors: *K. MCCABE[1], I. ATHAR[1], T. MAKANSI[3], A. J. FUGLEVAND[2];
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Abstract: Functional electrical stimulation (FES) is a rehabilitative technology involving artificial activation of paralyzed muscles that holds great promise to restore movement, health, and independence in those afflicted with high level spinal cord injuries. That potential, however, has not been realized because of significant limitations hindering its adoption. One significant limitation is the substantial cost and complexity associated with surgically implanting multiple FES electrodes needed to control movements of the paralyzed hand. To address this limitation, we have developed wireless, miniature (1 x 9 mm) stimulators that are injected through a needle directly into skeletal muscle without incisions. These stimulators are energized electromagnetically by small inductive transmitter coils placed on the skin above the injection site. Eighteen forearm and hand muscles of a rhesus macaque were implanted with these wireless stimulators. Coils (19 - 32 mm diameter) were secured within an elastic sleeve, and each coil was independently controlled by a multichannel programmable pulse generator. Stimulus waveforms consisted of a sequence of narrow, cathodic pulses that decayed in amplitude exponentially over ~100 μs followed by a single long anodal pulse. These waveforms were delivered at 40 Hz with continuously controllable amplitudes up to 40 V. We achieved robust, repeatable, and selective

activation of target muscles using stimulators at depths of up to 3 cm below the skin surface. This depth enables targeting of most forearm and hand muscles. These results demonstrate the feasibility of a wireless, miniature, injectable system for FES that could be deployed to restore hand function in individuals with tetraplegia.

Disclosures: K. McCabe: None. **I. Athar:** None. **T. Makansi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); StimAire. **A.J. Fuglevand:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); StimAire Inc..

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.08/AA11

Topic: F.05. Brain-Machine Interface

Support: Office of The Director (OD)
Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD)
National Institute Of Dental & Craniofacial Research (NIDCR) of the National Institutes of Health (NIH) under Award Number DP5OD029571 awarded to J.A.G.
Sponsorship was provided by the NSF Graduate Research Fellowship Program Award No.2139322 awarded to W.C.H.
This research was supported in part by Myomo Inc.

Title: Long-Term Use of an Assistive Myoelectric Orthosis Improves Functional Dexterity Relative to Conventional Standard-of-Care Therapy in Chronic Stroke Survivors

Authors: *L. M. FERRISI[1], W. C. HAMRICK[2], L. SECKINGER[3], D. LANGILLE[3], V. HOLMES[3], G. MERKOW[4], S. R. EDGLEY[5], A. SETHI[6], J. A. GEORGE[2];
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Abstract: Wearable myoelectric orthoses can assist stroke survivors with chronic upper-limb hemiparesis to support a weak arm while completing daily activities. Prior studies have reported improvement in functional dexterity, motor control, and patient-reported quality of life. However, most studies have been limited in sample size and duration. We are conducting a randomized controlled clinical trial (N=50 chronic stroke survivors) to evaluate the effectiveness of powered upper-extremity bracing using the MyoPro® myoelectric orthosis relative to standard-of-care therapy. The control group receives conventional in-clinic occupational therapy

with prescribed at-home exercises, as is standard of care. The interventional group receives similar therapy and home exercises but is given a functional myoelectric orthosis to use in clinic and at home to support their activities and home-based therapy. Here, we report on preliminary data from the first 14 enrolled participants at 2 months and 4 months post-enrollment. At 2 months, the interventional group showed significant improvements in functional dexterity when using the orthosis, with a +17.78-point improvement on the Chedoke Arm and Hand Activity Inventory (CAHAI) relative to baseline, far exceeding the MDC of 6 points. This improvement was significantly greater than the change observed in the control group (+0.60 points). At 4 months, the intervention group demonstrated continued improvement (+24.17 points relative to baseline), maintaining a statistically significant advantage over the control group (+2.00 points). Several patients, in both the interventional and control groups, met MDC and MCID thresholds for the Fugl-Meyer Assessment for the Upper Extremity (FMA-UE) of motor control, the Canadian Occupational Performance Measure (COPM) of self-reported patient satisfaction, and the Stroke Impact Scale of quality of life; however, between-group differences on these secondary measures were not significant in this preliminary cohort. These early findings suggest that combining an assistive myoelectric orthosis with goal-oriented therapy may be associated with greater improvements in functional dexterity than standard-of-care therapy alone. Continued enrollment and longer-duration follow-up are ongoing to determine the durability, clinical significance, and generalizability of these findings in the full randomized controlled trial cohort.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.09/AA12

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS Grant R01NS119160
NIH NINDS Grant R21NS128685
NSF DBI 2015317

Title: Direct brain control of artificial-muscle-based and muscle mimicking robots

Authors: D. M. TAYLOR[1,2,4], C. JACKSON[3], T. JOHNSON[2,1,4], Z. LUO[2,4], S. MORALLE[4], E. L. GRACZYK[2,1], B. AJIBOYE[2,1], ***R. D. QUINN**[3];

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Abstract: Motor-based Brain-Machine Interfaces (BMI) provide a means to control devices after paralysis using one's cortical activity associated with attempted reaching. Cortical activity has been used to control the motion of computer cursors, robotic arms, and even one's own paralyzed arm reanimated via neuromuscular stimulation. Different parts of the sensorimotor processing stream encode different aspects of movement such as intended velocity in Cartesian space and the muscle activations needed to achieve that desired motion. However, for some people, denervation or damage to the limb can limit the effectiveness of neuromuscular stimulation. For amputees, stimulation is also not an option. For these individuals, BMI-controlled assistive robotics and prosthetics can provide an intuitive means to restore reach and grasp function if the robot arm responds and interacts with the brain like a natural arm. Advancements in artificial-muscle-based robotics and muscle mimicking robot motors now make this possible. In this proof-of-concept study, we set out to develop a framework for BMI control of a biomimetic robot arm that could respond like a human muscle-actuated limb to BMI commands decoded in both Cartesian and muscle space. This process required integrating a real-time dynamic computational model of arm biomechanics and muscle activation properties with Westwood joint torque motors capable of mimicking these muscle effects in real time. A simulated BMI encoding either intended end-point velocity or directly encoding muscle activations was used to refine and validate the control of a muscle-mimicking robot arm with a BMI. A key advantage of muscle-mimicking robotics is the ability to modulate co-contraction to increase joint stiffness as needed for stabilization or to resist anticipated external forces. Muscle-based robotics may also facilitate natural proprioceptive feedback via intracortical microstimulation of Brodmann's area 3a by providing muscle-like information from the robot arm (e.g. muscle force, length and change in length) similar to what one would receive from a natural arm.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.10/AA13

Topic: F.05. Brain-Machine Interface

Support: NIH NS130397
University of Arizona Sensor Lab

Title: Noninvasive, hands-free control of an assistive robotic arm and comparison with an invasive brain machine interface

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Abstract: Recent advancements in assistive robotic arms have enabled many people with tetraplegia to perform activities of daily living more independently. Because these systems typically require hand use, they are not a ready option for many individuals with high-level tetraplegia. Such individuals, however, might be able to use signals that arise from the head and neck to control assistive devices. Previous work from our laboratory has shown that head-position control can support robotic reaching performance comparable to joystick-based hand control. Here, we evaluated the efficacy with which users could control a 6-DOF robotic arm using head motion for reaching and voice commands for gripping in a standardized task involving grasp, transport and placing of various objects. We also evaluated 1) the extent to which performance improved with practice, 2) whether those skills transferred to an untrained task, and 3) how performance on an object-transport task compared with published data involving an invasive brain-machine interface (BMI) (Collinger et al. Lancet 2013). Ten able-bodied participants completed six sessions using a 6-DOF robotic arm with gripper. The noninvasive interface combined a head position sensor to control reaching and voice commands for gripper control. During sessions 1 - 5, participants performed the Action Research Arm Test (ARAT) involving grasp, transport, and placing of various objects across multiple trials per session. The primary outcome measure was mean task completion time for each session. To assess how well training on this task transferred to another task, paricipants completed a timed Box-and-Block Test at the end of Sessions 1 and 5. In Session 6, participants performed a modified object-transport task designed to mimic that used in a study involving invasive BMI control of a robot arm. Mean (±SD) ARAT task completion time decreased from 37.0 ± 6.9 s in Session 1 to 20.7 ± 4.1 s in Session 5 ($p < 0.0001$). In the Box-and-Block Test, participants increased the number of blocks moved from 5.3 ± 0.8 in Session 1 to 7.8 ± 1.1 blocks in Session 5 ($p < 0.0001$). In Session 6, mean movement time using our noninvasive method involving head-motion and voice control was quicker (10.9 ± 1.3 s) than that measured over seven sessions in one patient using an invasive BMI (17.4 ± 4.9 s, $p = 0.0011$). These findings suggest that 1) over a few sessions, users significantly improved control of a 6-DOF assistive robotic arm with a noninvasive, hands-free interface, 2) such training transferred to an unpracticed skill, and 3) the noninvasive system performed more efficaciously than that of an invasive BMI system.

Disclosures: D. Noriega: None. **J. Alfaleh:** None. **A.J. Fuglevand:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.11/AA14

Topic: F.05. Brain-Machine Interface

Title: Closed loop dexterous hand movement via BCI-based Double Neural Bypass in Tetraplegia

Authors: *A. JANGAM[1], Z. ELIAS[2], E. IBROCI[3], C. BOUTON[1];
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Abstract: Restoration of upper arm and hand function is consistently ranked as the highest priority among individuals living with tetraplegia. Although significant progress has been made in decoding motor intentions to drive robotic arms or reanimate paralyzed limbs, achieving dexterous, individuated finger control remains a critical unmet challenge. We previously demonstrated that a nested neural architecture, combined with cortical sensory feedback, could restore functional task performance in real time for a participant with C4/C5 spinal cord injury, allowing precise grasping of fragile/soft objects. Here, we extend this work toward precision grasping by integrating three key innovations within a closed-loop decode-and-stimulate brain-body interface. First, we employ Neuromuscular Electrical Stimulation (NMES) of the upper limb to evoke precise, individuated digit movements. Using a Reinforcement Learning (RL) framework, we optimize the stimulation parameters, including electrode patterns, amplitude, and frequency, customized to the individual. Our initial trials demonstrated promising results, achieving 83.6% accuracy in producing targeted hand configurations. Second, the RL-optimized NMES is coupled in real time with decoded motor intentions, enabling the participant to shape their grasp according to object geometry and perform functional tasks requiring precision grip. Third, graded somatosensory feedback delivered to primary somatosensory cortex (S1) provides the participant with information about object compliance, allowing online modulation of grasp force. When blinded to visual cues, the participant distinguished among three objects of varying hardness based solely on cortical sensory feedback, achieving 64.3% accuracy. Together, these results demonstrate that a closed-loop decode-and-stimulate NMES system can restore not only volitional hand movement but also the sensory-guided dexterity essential for meaningful functional independence in individuals with tetraplegia.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.12/AA15

Topic: F.05. Brain-Machine Interface

Title: Closed-loop cursor control using intra-operative micro-ECoG recordings

Authors: *R. J. GREENE[1], K. LEHNER[3], S. LUO[2], D. CANDREA[2], R. ANUSHIRAVANI[4], Y. BYUN[4], M. MURPHY[5], J. DISTER[4], K. BARTH[4], E. HO[4], E. GHORPADE[6], F. CLAUDI[4], C. MERMEL[7], B. I. RAPOPORT[8], N. E. CRONE[9];

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Abstract: Brain-computer interfaces capable of continuous two-dimensional cursor control could restore digital access for people with paralysis, but high-fidelity decoding from cortical surface recordings has remained limited. Here, we show that high-density µECoG captures directional motor information sufficient for intuitive cursor control in humans. A 1,024-channel thin-film µECoG array (Precision Neuroscience, New York NY) was placed intraoperatively over hand motor cortex in four participants undergoing awake craniotomy for tumor resection. Participants performed a 2D target acquisition task requiring cursor movements toward visual targets. Participants first completed ~15 minutes of tasks by controlling cursor velocity with a contralateral joystick. This data was used to train participant-specific decoders mapping high-gamma activity to cursor velocity. Participants then spent ~4 minutes completing the task with cursor motion driven by real-time closed-loop neural decoding. The first two participants performed a 4-8 direction center out task. A directional classifier was trained and then utilized for discrete online control of a cursor in four-directions. P1 achieved 24.3% class-weighted accuracy (9 of 37), with successes largely restricted to the upwards direction. P2 achieved 68.3% class-weighted accuracy (21 of 35), with reliable down- and leftward decoding. These results, combined with the strong directional content in offline analyses, motivated a transition to continuous cursor control. The second two participants performed an eight-directional center-out task (P3), or a grid target task (P4), then used trained decoders for closed-loop continuous cursor control. We evaluated performance by measuring target acquisition rate and median completion time relative to joystick-based control during open-loop training sessions. This ratio provides a clinically interpretable, device-agnostic measure of BCI usability that reflects decoding accuracy and control. For P3, performance was biased toward rightward movements, with 47% of trials completed (8 of 17). Successful target acquisition required a median 10.71s, in comparison to 7.22s for tasks completed with the joystick. P4 completed 91.7% of trials (75 of 82) with a median completion time of 3.52s (2.66s with joystick). These findings establish µECoG as a platform that combines directional information (previously only accessible through penetrating electrodes) with the safety and stability advantages of a surface-based recording system. This approach could offer a scalable path toward restoring independence for people with severe motor disability.

Disclosures: R.J. Greene: None. **K. Lehner:** None. **S. Luo:** None. **D. Candrea:** None. **R. Anushiravani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscience. **Y. Byun:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscience. **M. Murphy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscience. **J. Dister:** A. Employment/Salary (full or part-time):; Precision Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision Neuroscience. **K. Barth:** A. Employment/Salary (full or part-time):; Precision Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Precision

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.13/AA16

Topic: F.05. Brain-Machine Interface

Support: DoD CDMRP SC180308
VAMR 5I01RX002654

Title: High-Fidelity FES Elbow Control in Human Tetraplegia Achieved Through Phenomenological Muscle Modeling

Authors: *J. KRALL[1,2], B. HUTCHISON[2], B. ALEXANDER[2], W. MEMBERG[2,4], R. F. KIRSCH[2,3,4], B. AJIBOYE[2,3,4];
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Abstract: Functional Electrical Stimulation (FES) can be used to reanimate paralyzed limbs and restore volitional movement to individuals with tetraplegia. Commonly, desired kinematic outputs are mapped to stimulus parameters using a static lookup table. However, predicting muscle behavior is non-trivial due to non-linear recruitment and history-dependent properties, such as thixotropy and hysteresis, which degrade control accuracy. To address this, we designed, implemented, and validated a novel FES controller that combines a phenomenological feedforward muscle model with a feedback element. The controller is calibrated by mapping the stimulus-to-joint position relationship as the joint is slowly cycled between full extension and flexion. The resulting major ascending and descending hysteresis curves are modeled using

Piecewise Cubic Hermite Interpolating Polynomials (PCHIP). Furthermore, the interior of the hysteresis loop is modeled utilizing Madelung's Rules, restricted to a single turning point for computational efficiency, to effectively linearize the muscle response. Any remaining unmodeled dynamics are compensated for by a proportional-integral (PI) feedback controller running in parallel. We validated the new controller against a legacy lookup table-based system (which relied solely on the ascending curve) in a human participant with tetraplegia, specifically modulating FES-induced bicep activation to control elbow joint position. The novel controller significantly outperformed the legacy system, yielding lower Root Mean Square Errors (RMSE, expressed as a percentage of the total range of motion) in a Major Loop Tracking test (full extension-to-flexion cycling; 4.59% vs. 18.11%), a Minor Loop Tracking test (incorporating mid-range directional changes; 9.53% vs. 19.09%), and a Velocity Sweep Tracking test (11.57% vs. 36.66%). Future work will integrate this robust FES controller into a closed-loop brain-machine interface (BMI) to enable individuals with cervical spinal cord injuries to precisely control paralyzed limbs, with broader applications in lower-limb gait control and dexterous grasping.

Disclosures: J. Krall: None. **B. Hutchison:** None. **B. Alexander:** None. **W. Memberg:** None. **R.F. Kirsch:** None. **B. Ajiboye:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.14/AA17

Topic: F.05. Brain-Machine Interface

Support: ASSIST RERC, 90REGE0017-01
HCC_2106747

Title: Finger-specific motor intention decoding from high density electromyography

Authors: *A. SHAHROOEI[1], O. PATEL[2], D. G. KAMPER[3];
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Abstract: High-density surface electromyography (HD-sEMG) can provide an intuitive means for controlling an assistive device, such as a hand exoskeleton. Here, we developed a motor intention decoding framework to estimate desired isometric fingertip force for index and middle fingers from HD-sEMG signals. Separate models were created for the index and middle fingers. We were especially interested in this study about running these models in parallel, i.e. how each finger's model performs in the trials where the other finger is intentionally activated. A participant performed prescribed isometric force generation of the index and middle fingers; the reference signal was a trapezoidal waveform with varying amplitude and visual feedback of measured force was provided in real-time. HD-sEMG was recorded from 128 volar and 64 dorsal

forearm channels at 2048 Hz and synchronized with the force data. HD-sEMG signals were decomposed into firing rates for individual motor units using blind-source separation (FastICA) followed by binary classification. For isometric force decoding, motor units were assigned to one of four task-specific clusters: index flexion, index extension, middle flexion, and middle extension. Four linear models were trained independently and then combined to estimate index and middle fingertip forces. Testing used held-out trials that were not used for channel selection, motor unit extraction, motor unit assignment, or model fitting. For isometric force estimation, the index model achieved root mean squared error (RMSE) = 11.8 % maximum voluntary force (MVF), while the middle finger model achieved RMSE = 12.0 %MVF. Predicted trajectories followed the main temporal patterns of the measured force across held-out trials. The models still predict substantial force values in the test trials where their associated finger is not the intended finger. This cross-finger prediction performance is one of the challenges we will try to resolve in our next steps through improving our motor unit clustering algorithm. This framework provides an interpretable step toward HD-sEMG-based neural interfaces for real-time control of assistive hand devices.

Disclosures: A. Shahrooei: None. **O. Patel:** None. **D.G. Kamper:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.15/AA18

Topic: F.05. Brain-Machine Interface

Support: ASSET RERC 90REGE0017-01

Title: Examination of Control Schemes for an Assistive Hand Exoskeleton

Authors: *C. M. VOGEL[1], D. G. KAMPER[2];
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Abstract: Despite extensive therapeutic efforts, roughly half of all stroke survivors will experience chronic impairment. This typically involves the hand, which leads to substantial functional deficits in performing daily activities of living. As such, assistive devices, such as hand exoskeletons, may prove beneficial for restoring function for individuals post-stroke. To be effective, however, the device must be controllable in a facile manner that encourages usage. An ideal control strategy alleviates cognitive demand for the user and therefore provides an interface that is more intuitive for individuals with motor impairment. To investigate this, we have developed a user interface for controlling a custom hand exoskeleton (BAC-Glove). The BAC-Glove provides bidirectional (flexion/extension) actuation of each digit independently. Flexible metal cables run through guides on the dorsal side of the hand and transfer force to the digits

from linear servomotors on the forearm. The wearable, portable device is operated through an embedded microcontroller (PIC32). The user interface provides two-stage control. First one of four grasp patterns is chosen on the touch screen: whole-hand gasp, two-finger gasp, three-finger grasp, and index finger point. Next, the second stage allows continuous specification of either desired position or velocity by moving a slider bar on the screen. We are comparing use of position or velocity as the control variable. Participants with chronic impairment post-stroke experience both the position and velocity-control modes. After a practice session, the participant performs a series of clinical assessments, controlling the BAC-Glove with an assigned mode: a subset of the Action Research Arm Test (ARAT), Box and Block Test (BBT), and transport of a fragile eggshell. Participants also perform the tasks without the BAC-Glove. Test condition order is randomized for each participant. At the end of the session, each participant completes a questionnaire on perceived ease of use, intuitiveness, and preference for the BAC-Glove and the application/control modes used to control it. We anticipate that both control modes with the BAC-Glove will improve task performance relative to the no-device condition, with position-based control having better performance and usability outcomes compared to velocity-based control. These results will help guide development of assistive devices by identifying user-control strategies that maximize functional performance with hand exoskeletons, which may improve quality of life for individuals after stroke.

Disclosures: C.M. Vogel: None. **D.G. Kamper:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.16/Web Only

Topic: F.05. Brain-Machine Interface

Support: TUBITAK GRANT#: 123E713

Title: Comparing EEG, EMG, and IMU Signals for Gait Event Prediction in Functional Electrical Stimulation

Authors: *E. CURUK[1], A. SARIKAS[2], I. OZTURK[3], M. PINAR[2], G. KARA[4], U. BASPINAR[2], F. M. ISLAH[5], E. PINAR[6];
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Abstract: Functional electrical stimulation (FES) for drop-foot correction requires accurate gait-event timing. Dorsiflexion assistance can be modulated within the clinically relevant swing-phase interval. Although multimodal sensing is often predict to improve FES timing, it remains unclear whether full EEG-EMG-IMU fusion provides a meaningful advantage over compact single-modality sensing configurations. In this study, we systematically compared EEG,

unilateral EMG, IMU, and their combinations for FES-oriented heel-strike/toe-off (HS/TO) timing estimation using a multi-input Bidirectional Long Short-Term Memory (BiLSTM) framework. Electroencephalography (EEG) from three motor-cortex channels (Cz, C3, and C4), unilateral surface electromyography from the tibialis anterior (TA) and soleus (SOL) muscles, and inertial measurements (IMUs) sensors placed on the same lower limb were collected from 15 participants, including 9 individuals with drop-foot and 6 healthy controls. The final dataset contained 3,918 valid cycle-level windows. EEG, EMG, and IMU inputs were represented as fixed-length temporal tensors of (250, 3), (250, 2), and (30, 18), respectively. A multi-input BiLSTM model was trained to estimate cycle-relative HS and TO timings as two continuous regression targets, and seven modality configurations were compared under leave-one-subject-out cross-validation. Six configurations clustered within a narrow TO timing-error range of 109.0-116.3 ms, and none differed significantly from the EMG-only model after correction for multiple comparisons. EMG-only achieved the lowest mean error (109.0 ± 20.1 ms), whereas IMU-only (112.4 ± 28.4 ms) and full multimodal fusion (115.1 ± 33.0 ms) remained statistically comparable ($p > 0.05$; Cohen's $d < 0.3$). EEG-only was less reliable (164.7 ± 94.1 ms; $p = 0.03$), suggesting that cortical signals alone were insufficiently precise for cycle-level event timing in this cohort. All non-EEG-only configurations preserved mean residual safety margins greater than 250 ms relative to a nominal 400 ms FES timing requirement. These results suggest that optimized EMG-only or IMU-only sensing may provide timing information comparable to full multimodal fusion for FES-oriented HS/TO timing estimation. However, the present findings should be interpreted as offline cycle-level evidence; strictly causal sliding-window validation and closed-loop FES-assisted walking experiments are required before real-time deployment recommendations can be made.

Disclosures: E. Curuk: None. **A. Sarikas:** None. **I. Ozturk:** None. **M. Pinar:** None. **G. Kara:** None. **U. Baspinar:** None. **F.M. Islah:** None. **E. Pinar:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.17/AA19

Topic: F.05. Brain-Machine Interface

Support: Air Force Office of Scientific Research (Award No. FA9550-24-1- 0208)

Title: Hidden computational structure in musculoskeletal dynamics

Authors: *S. YAKOVENKO;
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Abstract: Accurate forward simulation of musculoskeletal systems is challenged by the rapidly increasing structural complexity of articulated bodies, where additional segments, joints, and musculotendon pathways substantially expand the dimensionality of the governing equations.

Conventional approaches often assume that computational requirements scale steeply with model complexity, reflecting the growth of nonlinear interactions among system components. Here, this approach demonstrates that a physics-embedded recurrent neural network can efficiently represent the dynamics of structurally complex biomechanical systems without exhibiting exponential growth in network size or computational cost. Extending analyses from musculoskeletal coordinate transformations to the dynamics of multi-segment arm and hand models, we find that the required recurrent architecture for inverse and forward simulations scales linearly relative to the increase in mechanical degrees of freedom and model parameters. This result suggests that the governing structure of movement mechanics possesses latent computational regularities that can be exploited by appropriately constrained recurrent architectures. We propose that these regularities arise from the existence of efficient reference frames and hierarchical coordinate representations embedded within the mechanics of biological movement itself. Such representations reduce the effective dimensionality of dynamic computations by organizing interactions into locally structured transformations rather than fully combinatorial relationships. The observed scaling behavior further suggests that musculoskeletal anatomy may embody computational principles that facilitate efficient neural control and prediction. Together, these findings support the view that biomechanical dynamics possess an intrinsic low-dimensional organization and that physics-embedded recurrent networks can leverage this structure to achieve scalable forward simulation of increasingly complex neuromechanical systems.

Disclosures: S. Yakovenko: None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.18/AA20

Topic: F.05. Brain-Machine Interface

Support: Biological Input Output Systems
Utah ONE-U Responsible AI Initiative

Title: Closed-loop Upper-Limb Neuroprosthesis Improves Functionality and Independence for Transradial Amputee Patient

Authors: *M. A. TROUT[1], F. MINO[5], T. TULLY[2], L. FERRISI[3], W. C. HAMRICK[6], L. SECKINGER[7], D. LANGILLE[7], T. DAVIS[8], D. HUTCHINSON[9], J. A. GEORGE[4,10,11,7]; [1]Scientific Computing Inst., Univ. of Utah, Salt Lake City, UT; [2]Electrical and Computer Engin., Univ. of Utah, Salt lake City, UT; [3]Biomed. Engin., [4]Electrical and Computer Engin., Univ. of Utah, Salt Lake City, UT; [5]Electrical and Computer Engin., The Univ. of Utah, Salt Lake City, UT; [6]Univ. of Utah, Dept. of Electrical and Computer Engin., Salt Lake City, UT; [7]Physical Med. and Rehabil., [8]Neurosurg., [9]Orthopedic Surgery, [10]Biomed. Engin., [11]Mechanical Engin., Univ. Of Utah, Salt Lake City, UT

Abstract: Prostheses are now capable of mimicking the movements of endogenous human hands, but the methods for controlling and receiving feedback from prostheses are still inadequate. The advent of neuromuscular implant systems capable of recording efferent motor activity and stimulating afferent sensory nerve fibers improves the transfer of sensorimotor information to and from a user's peripheral nervous system, paving the way for more dexterous prosthetic control. Over the last decade, we have been developing a neuroprosthesis that uses Utah Slanted Electrode Arrays (USEAs) and intramuscular electromyographic leads (iEMGs) implanted into the residual arm nerves and muscles, respectively. Our work with now 9 transradial amputees has shown that the neuroprosthesis is safe, evokes natural-feeling sensations, and provides intuitive prosthetic control, collectively improving dexterity, reducing phantom pain, and fostering a sense of embodiment. Here, we present initial data from our 9th participant, a 32-year-old male who had a transradial amputation 16 years ago and had USEAs and iEMGs implanted 4 months ago. Two USEAs were implanted in the median nerve, and one USEA in the ulnar nerve. Each USEA (Blackrock Neurotech) consists of a 10×10 electrode grid, with electrodes 0.75 to 1.5 mm in length. Eight, bipolar iEMGs (Synapse Biomedical) were implanted into the participant's residual extrinsic hand muscles in the forearm. At 15-weeks post implant, USEAs continued to provide meaningful impedances, single-unit neural recordings, and sensory percepts. Custom attachments and processors (BIOS) were integrated to the neural interface processor (Ripple) to allow the participant to independently don and doff the system with their contralateral limb. The participant completed one week of occupational therapy (OT) with the neuroprosthesis centered around goals identified via the Canadian Occupational Performance Measure (COPM). Within one week, performance and satisfaction scores on the COPM increased from 3.2 and 2.2, to 8.3 and 9.3, respectively. Notable activities performed with the neuroprosthesis include cutting blackberries, drinking from a paper cup, and making an omelet. These preliminary results highlight the potential benefits in patient-reported outcomes when using a neuroprosthesis in conjunction with goal-oriented OT. Future work is ongoing to assess the impact of long-term use of upper-limb sensorimotor function and quality of life.

Disclosures: M.A. Trout: None. **F. Mino:** None. **T. Tully:** None. **L. Ferrisi:** None. **W.C. Hamrick:** None. **L. Seckinger:** None. **D. Langille:** None. **T. Davis:** None. **D. Hutchinson:** 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.; BIOS. **J.A. George:** 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.; BIOS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BIOS. F. Consulting Fees (e.g., advisory boards); BIOS.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.19/AA21

Topic: F.05. Brain-Machine Interface

Support: Biological Input/Output Systems
DARPA BTO HAPTIX #N66001-15-C-4017
NIH DP5-OD029571
NSF CHS-1901492, NSF NCS-FO-1533649

Title: Longitudinal Comparison of Neural Feature Extraction to Improve Long-Term Simultaneous Proportional Control of Multi-Degree-of-Freedom Prosthetic Hands via Peripheral Nerve Interfaces

Authors: *F. MINO[1], B. MECHAM[3], P. T. ZAMANI[4], T. DAVIS[5], D. J. WARREN[8], D. HUTCHINSON[6], G. A. CLARK[2], J. A. GEORGE[7];
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Abstract: The long-term goal of this research is to improve the functional lifespan of bidirectional peripheral nerve interfaces for upper-limb prosthetic control. Approximately 700,000 individuals in the United States live with upper-limb loss, and advanced prostheses that leverage peripheral nerve interfaces to restore dexterous control are becoming increasingly common. In particular, bidirectional invasive interfaces like the Utah Slanted Electrode Array (USEA) offer the advantage of providing highly localized, natural sensory percepts and recording single-unit action potentials. Historically, the recording capabilities of the USEA have been used to estimate features like Neural Firing Rates (NFR), enabling simultaneous proportional control of multi-degree-of-freedom (DOF) prostheses. However, the ability to record individual spikes has also been shown to decline over time, thus negatively impacting the long-term performance of NFR-based prosthetic control.This study compares three alternative neural features that do not require spike detection—Discrete Wavelet Transform (DWT), Spiking Band Power (SBP), and Mean Absolute Value (MAV)—against NFR for multi-DOF prosthetic control. Data was collected longitudinally from three participants with USEAs implanted for several months. Feature performance was evaluated offline using intended root mean square error (RMSE) in simultaneous proportional control tasks of increasing complexity (3-, 6-, and 8-DOF). A linear mixed-effects model assessed the effects of task complexity, feature type, time, and their interaction on RMSE, with trials and sessions nested within participants as random effects. Term significance was determined via likelihood ratio tests, and post-hoc pairwise comparisons used Tukey-Kramer correction.Using a Kalman Filter, DWT achieved significantly smaller RMSE (0.398) than NFR (0.456, $p < 0.001$, $d=0.464$), SBP (0.452, $p<0.001$, $d=0.433$), and MAV (0.475, $p < 0.001$, $d=0.616$). All features exhibited significant performance degradation over time ($p < 0.001$). A significant feature-by-time interaction ($p < 0.001$) revealed that DWT and SBP degraded more rapidly than NFR and MAV, the latter of which demonstrated the most consistent long-term performance despite higher prediction error.These offline findings suggest that DWT may provide superior online decoding accuracy during early implant life, while MAV may offer slower degradation at some expense of performance. Understanding these tradeoffs may guide future feature extraction and adaptive feature-selection strategies aimed at extending the usable lifespan of peripheral nerve interfaces for prosthesis control.

Disclosures: F. Mino: None. **B. Mecham:** None. **P.T. Zamani:** None. **T. Davis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder, University of Utah. **D.J. Warren:** 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.; BIOS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder, University of Utah. F. Consulting Fees (e.g., advisory boards); Blackrock. **D. Hutchinson:** 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.; BIOS. **G.A. Clark:** 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.; BIOS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder, University of Utah. F. Consulting Fees (e.g., advisory boards); BIOS. **J.A. George:** 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.; BIOS. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder, University of Utah, Equity Holder, BIOS. F. Consulting Fees (e.g., advisory boards); BIOS.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.20/AA22

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UG3NS123135

Title: Why 40Hz? A Mechanistic Framework to Understand Optimal Spinal Cord Stimulation for Motor Control

Authors: *J. OSTROWSKI[1], G. PRAT ORTEGA[2], M. CAPOGROSSO[3];
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Abstract: Epidural spinal cord stimulation (SCS) is a novel therapeutic technique that promises to dramatically help patients regain voluntary motor control following injury to the motor system, such as stroke and spinal cord injury. In epidural SCS, electrodes placed on the spinal cord activate proprioceptive fibers, which synapse onto the motoneurons and cause transient subthreshold depolarizations of the motoneuron membrane (Capogrosso et al., 2013). Recovery

of volitional motor control is possible due to the summation of these inputs with the limited descending signal available from the brain post-injury (Balaguer et al., 2025). Despite this mechanistic understanding, it is still unknown why stimulation frequencies in the 40-80 Hz range are consistently observed to be optimal in clinical applications of SCS for motor control (e.g. Harkema et al., 2011; Carhart et al., 2004; etc.).
Here, we consider how the dynamics of the underlying spinal circuitry result in this frequency-dependent efficacy. We present experimental evidence that highlights two crucial phenomena impacting the transmission of stimulation: rate-dependent depression and temporal summation of EPSPs. Rate-dependent depression (RDD) refers to the depletion of neurotransmitter at the synapse; as SCS frequency increases, more stimulation-evoked spikes fail to propagate due to a lack of available neurotransmitter, ultimately reducing the effective input to the motoneuron pool. Conversely, we show data to indicate that SCS produces elongated EPSPs in the motoneuron membrane, likely through circuit-level activation, which summate towards firing threshold more rapidly as the frequency of stimulation increases. We integrate these two phenomena into an existing model of SCS in order to show that, when considering these dynamics, stimulation in the 40-80Hz range optimizes the ability of the brain to volitionally control stimulation within the confines imposed by the underlying circuitry. Lastly, we present evidence from patients with implanted epidural leads that confirms the frequency-dependent effects of SCS and highlights the importance of stimulation parameters in therapeutic applications of SCS for regaining motor control.

Disclosures: J. Ostrowski: None. **G. Prat Ortega:** None. **M. Capogrosso:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.21/AA23

Topic: F.05. Brain-Machine Interface

Support: This project was supported by Neuralink

Title: High-density intraspinal microstimulation for restoring dexterous hand control

Authors: *E. ROGERS[1], L. TONI[7], N. MACELLARI[2], R. KUMAR[8], L. LIANG[3], P. GERSZTEN[4], E. PIRONDINI[5], J. E. O'DOHERTY[9], M. CAPOGROSSO[6];
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Abstract: Restoring hand function is the top clinical priority for patients with upper limb paralysis, yet no current neuroprosthetic meets this need. Cervical intraspinal microstimulation (ISMS) is a promising technique for restoring dexterous hand control but its development has

been limited by non-selective muscular co-activation and a lack of somatotopically-appropriate recruitment (i.e, muscles activation not following the known rostro-caudal distribution of their motor pools). We hypothesized that a high spatial density approach, combined with careful parameter titration, could overcome these challenges and produce highly selective activation of hand musculature in a somatotopically-appropriate fashion by avoiding off-target axonal activation. We tested our hypothesis in vivo in n = 2 macaques. Specifically, we used Neuralink's surgical robot to semi-automatically implant >100 electrode threads in the lower cervical spinal cord while recording intramuscular electromyography from hand and arm muscles, then performed a parameter sweep evaluating muscle recruitment for various combinations of amplitude, frequency, polarity, electrode thread, and stimulating contact. We found that evoked responses were highly sensitive to all tested parameters. In line with our hypothesis, a subset of parameter combinations produced selective recruitment of intrinsic hand muscles, as well as functional synergistic movements including multi-finger closing/opening and wrist/forearm rotation. Stimulation frequencies below ~200 Hz produced increasingly strong but somatotopically-appropriate recruitment patterns, whereas higher frequencies produced spread to other muscles innervated by other spinal levels, offering a potential mechanistic explanation for the lack of somatotopy observed in previous investigations. Using the same contact, switching between anodic and cathodic stimulation changed which muscles were activated by stimulation, indicating stimulation polarity can act functionally to expand the range of induced movements from a fixed number of electrodes. Additionally, EMG responses showed a combination of modulated and non-modulated responses during elevated stimulation frequencies, indicating the capability for ISMS to both directly and indirectly activate motoneurons depending on electrode position. Overall, our results clearly demonstrate the capability for ISMS to generate highly selective recruitment of hand musculature, supporting the potential for this therapy as a clinical neuroprosthetic for upper limb paralysis and guiding future parameter selection.

Disclosures: E. Rogers: None. **L. Toni:** None. **N. Macellari:** None. **R. Kumar:** A. Employment/Salary (full or part-time):; Neuralink. **L. Liang:** None. **P. Gerszten:** None. **E. Pirondini:** None. **J.E. O'Doherty:** A. Employment/Salary (full or part-time):; Neuralink. **M. Capogrosso:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Neuralink.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.22/AA24

Topic: F.05. Brain-Machine Interface

Support: University of Pittsburgh Clinical Translational Science Institute
University of Pittsburgh Pitt SPARK
University of Pittsburgh Medical Center Beckwith Institute
PNRR PA scholarship

Title: Which motor thalamic nucleus best facilitates speech? Intraoperative mapping and behavioral testing with Deep Brain Stimulation in patients with brain lesions

Authors: *V. FOSSATI[1,2], J. E. TING[3], C. GOSWAMI[2], A. DAMIANI[3], N. MACELLARI[4], L. TANG[2], L. PIVETTI[2], S. NOUDURI[2], E. M. GRIGSBY[3], J. HO[5], S. ENSEL[2], G. F. WITTENBERG[6], D. J. CRAMMOND[7], K. STIPANCIC[10], J. A. GONZÁLEZ-MARTÍNEZ[8], E. PIRONDINI[9];
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Abstract: Brain lesions can affect the corticobulbar tract (CBT) and corticospinal tract (CST), disrupting motor cortex output to cranial and spinal muscles. When the CBT is affected, patients develop orofacial weakness and speech disorders, and these deficits remain largely refractory to rehabilitation. We previously demonstrated that low-frequency (50-80 Hz) deep brain stimulation (DBS) of the motor thalamus increases cortical excitability and potentiates CBT output, producing immediate improvements in speech quality. However, the motor thalamus comprises anatomically and functionally distinct nuclei, the ventral oralis posterior (VOP), ventral oralis anterior (VOA), and ventral intermediate nucleus (VIM), and it remains unclear which nucleus constitutes the optimal stimulation target for facilitating speech motor output. To address this question, four participants with brain injury and chronic speech deficits were included: one with traumatic brain injury and a pre-existing DBS implant at the VIM/VOP boundary for essential tremor, and three with cortical stroke who underwent temporary motor thalamic DBS implantation. Intraoperatively, microelectrodes were passed through the VOA, VOP, and VIM nuclei to record neural activity at multiple depths while participants performed facial and speech tasks. We then assessed single-nucleus thalamic stimulation by pairing DBS with direct cortical stimulation (DCS) of face primary motor cortex and measuring motor-evoked potentials (MEPs) of facial muscles. Based on this mapping, the DBS electrode was implanted at the target showing the strongest face motor representation. During post-implantation assessments, stimulation protocols steering current across nuclei were delivered, and we evaluated speech quality using tasks including diadochokinesis (DDK) and word and sentence repetition, orofacial muscle strength using the Iowa Oral Performance Instrument (IOPI), and facial muscle function through standardized facial expression tasks. Intraoperative recordings identified VOP and VOA as the nuclei with the strongest face motor output, with MEP potentiation most consistently observed during VOP stimulation, suggesting preferential facilitation of corticobulbar pathways. Post-implantation assessments suggested a divergent pattern, with VIM stimulation showing trends toward functional improvements, suggesting that intraoperative electrophysiological markers may not fully predict functional outcomes. These findings provide initial evidence toward identifying the optimal thalamic target for DBS-mediated facilitation of motor speech in individuals with brain lesions.

Disclosures: V. Fossati: None. **J.E. Ting:** None. **C. Goswami:** None. **A. Damiani:** None. **N. Macellari:** None. **L. Tang:** None. **L. Pivetti:** None. **S. Nouduri:** None. **E.M. Grigsby:** None. **J. Ho:** None. **S. Ensel:** None. **G.F. Wittenberg:** None. **D.J. Crammond:** None. **K. Stipancic:** None. **J.A. González-Martínez:** None. **E. Pirondini:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.23/AA25

Topic: F.05. Brain-Machine Interface

Support: Spinal Muscular Atrophy Foundation

Title: Rethinking Fatigue in Spinal Muscular Atrophy: Motor Unit Types and Their Contribution to Endurance and Fatigability

Authors: *S. DONADIO[1,5,2], J. OSTROWSKI[6,5], E. PIRONDINI[3,2,5], G. PRAT ORTEGA[4,2,5], M. CAPOGROSSO[4,2,5];
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Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative disorder caused by SMN1 gene loss, leading to motoneuron (MN) dysfunction, death, and severe muscle weakness. People with SMA also report high levels of fatigue, yet current clinical tests rarely account for relative effort: because of muscle weakness, everyday activities require greater effort than healthy individuals.Thus,whether fatigue reflects a distinct mechanism or is driven by muscle weakness remains unclear.Preclinical studies have shown that SMA MNs exhibit reduced firing rates, and autopsy studies in individuals with SMA have reported preferential loss of fast-fatigable motor units (MUs). We previously found that 4 weeks of spinal cord stimulation (SCS) can reverse MN dysfunction, increase MN firing rates, and improve strength in ambulatory SMA adults. However, its effect on fatigue remains unknown.Here, we hypothesized that people with SMA would show an abnormally fatigue-resistant profile compared to healthy controls (HCs). Additionally, since SCS increases MN firing rates, we hypothesized that SCS would shift SMA fatigability toward a healthier profile. To test these hypotheses, we developed an effort-normalized protocol consisting of repeated maximal voluntary contractions (MVCs). During each MVC, transcranial magnetic stimulation (TMS) was delivered to assess central fatigue, while motor unit conduction velocity (MUCV) was estimated as an index of peripheral fatigue. The protocol was tested in n=2 non-ambulatory SMA and n=3 HCs to characterize the SMA fatigue profile, and then repeated after 4 weeks of SCS to evaluate the changes induced by SCS.SMA participants were less fatigable than HCs, as shown by the percent change in peak force across MVCs (FI: SMA6= -26.1%; HC1 = +49.2%). This fatigue-resistant profile was paralleled by stable TMS-evoked force twitches across MVCs in SMA, whereas HCs showed increasing TMS-evoked twitches during the fatigue protocol, consistent with greater central fatigue. SMA participants also showed lower MUCV than HCs, consistent with slower, more fatigue-resistant MU properties. After 4 weeks of SCS, SMA participants increased strength by up to 183% and shifted toward a healthier fatigability profile (SMA6 post-SCS FI = +17.7%) and higher MUCV. These changes suggest that by reversing MN dysfunction, SCS shifted the active MU pool toward faster, less fatigue-resistant properties. Together, these preliminary results suggest that fatigue in SMA may primarily reflect muscle weakness rather than a separate

pathological mechanism. By improving strength and restoring a more physiological fatigability profile, SCS may be explored as a treatment in SMA.

Disclosures: S. Donadio: None. **J. Ostrowski:** None. **E. Pirondini:** None. **G. Prat Ortega:** None. **M. Capogrosso:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.25/AA26

Topic: F.05. Brain-Machine Interface

Support: R01NS131428

Title: Deep Brain Stimulation of the Motor Thalamus Improves Dexterity and Fine Motor Control After Stroke

Authors: *A. DAMIANI[1], N. MACELLARI[2], Z. XU[3], C. GOSWAMI[1], C. JEZERC[4], L. LIANG[3], J. E. TING[5], L. PIVETTI[3], V. FOSSATI[9], S. NOUDURI[1], K. HOFFMANN[6], E. M. GRIGSBY[5], L. TANG[1], M. CAPOGROSSO[7], J. A. GONZÁLEZ-MARTÍNEZ[7], E. PIRONDINI[8];
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Abstract: In primates, dexterous motor control is heavily supported by the corticospinal tract (CST), the major descending motor cortical efferent pathway. Indeed, even small CST lesions can lead to permanent loss of finger, hand, and overall upper-limb dexterity. While neuromodulation approaches such as spinal cord stimulation can alleviate loss of strength and gross upper-limb function, no effective treatments exist to recover distal dexterity and fine motor control. Here, we hypothesized that a neurotechnology capable of facilitating residual CST axons could mitigate these symptoms. Therefore, we targeted deep brain stimulation (DBS) to the motor thalamus (mTh), a subcortical region with monosynaptic excitatory projections to the motor cortex (M1). First, we demonstrated in anesthetized monkeys that mTh-DBS potentiates M1 and CST excitability. We also confirmed that this facilitation occurs through M1, and not via direct subcortical projections to the spinal cord. Additionally, CST facilitation is maximal when stimulation is delivered directly to the thalamocortical fibers via the mTh, rather than trans-synaptically (e.g, through the cerebellum or basal ganglia). We then hypothesized that mTh-DBS increases CST excitability also during voluntary movement and thus alleviates post-stroke loss of dexterity. To test this hypothesis, we trained n=3 monkeys on tasks measuring hand and arm dexterity. We then performed a controlled thermocoagulation of the CST inducing mild-

moderate upper-limb paresis. During the same procedure, we implanted a DBS electrode in the mTh and assessed behavioral performances and kinematic variables with and without DBS, for up to 4 months post stroke. DBS immediately improved 3D dexterous arm and finger control, as evidenced by higher task success rate and enhanced reaching smoothness, endpoint precision, hand grasping and finger mobility. Finally, we replicated these results in n=3 human patients with chronic post-stroke hemiparesis, who received a temporary DBS implant in the mTh and were stimulated for 4 weeks, 2h per day during motor tasks. Our intervention led to immediate improvements in dexterity and range of motion, as well as increased strength across multiple joints. Notably, electrophysiological testing confirmed enhanced corticospinal excitability after only 4 weeks of DBS, as evidenced by the emergence of transcranial magnetic stimulation-induced motor evoked potentials in the forearm muscles. These findings demonstrate for the first time the potential of motor thalamus DBS to alleviate motor symptoms developed after stroke and pave the way towards novel therapies for the recovery of dexterous motor control.

Disclosures: A. Damiani: None. **N. Macellari:** None. **Z. Xu:** None. **C. Goswami:** None. **C. Jezerc:** None. **L. Liang:** None. **J.E. Ting:** None. **L. Pivetti:** None. **V. Fossati:** None. **S. Nouduri:** None. **K. Hoffmann:** None. **E.M. Grigsby:** None. **L. Tang:** None. **M. Capogrosso:** None. **J.A. González-Martínez:** None. **E. Pirondini:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.26/AA27

Topic: F.05. Brain-Machine Interface

Support: R01NS131428
R01NS122927

Title: From Suppression to Potentiation: Why High-Frequency Deep Brain Stimulation Suppresses but Low-Frequency Potentiates Cortical Activity

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Abstract: Conventionally, deep brain stimulation (DBS) is delivered clinically at ~130 Hz to suppress pathological cortical hyperexcitability, as in essential tremor. However, recently, DBS has also been proposed as a tool to potentiate brain activity rather than suppress it. A growing body of experimental evidence demonstrates that DBS at lower frequencies (50-80 Hz) potentiates cortical activity, revealing a stark dichotomy in the cortical response to DBS frequency. Yet the predominant focus in literature on high-frequency (100-130 Hz) stimulation

constrains our understanding of the neural processes that shape the cortical response to DBS, and in turn limits its viability as a brain-potentiation tool. Furthermore, known DBS mechanisms, such as information lesion and rate-dependent suppression, only partially account for this dichotomy, highlighting the need for their refinement. We utilize biophysical modeling, combined with cortical, spinal, and electromyographic recordings from non-human primates, to explain the cortical mechanisms underlying this dichotomy in the cortical response to DBS frequencies. Specifically, we construct a 3-population network model, consisting of pyramidal-tract projecting (PT) neurons, parvalbumin-expressing (PV) interneurons, and somatostatin-expressing (SST) interneurons representing layer 5 of the motor cortex. Our network model reproduces the dichotomous behavior of DBS, showing potentiation at low frequencies and suppression at high frequencies. Our model implicates SST interneurons as a key mediator of the cortical response to DBS frequencies. At high frequencies, SST interneurons suppress cortical activity via GABA-B receptors, while their inactivation at low frequencies allows excitatory inputs generated by DBS to consistently depolarize the cortex. We validate our claims by pharmacologically blocking GABA-B receptors, which completely removes the suppressive effects of high-frequency DBS. Our results elucidate distinct biophysical processes shaping the cortical response to DBS frequency. These mechanistic insights are crucial for appropriately tailoring DBS strategies to maximize the intended therapeutic outcomes. For example, low-frequency DBS may improve outcomes in conditions requiring boosted cortical activity (e.g., stroke, depression), while high-frequency DBS remains appropriate for suppressing pathological hyperexcitability (e.g., essential tremor, epilepsy).

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.27/AA28

Topic: F.05. Brain-Machine Interface

Support: University of Pittsburgh Clinical Translational Science Institute
University of Pittsburgh Pitt SPARK
University of Pittsburgh Medical Center Beckwith Institute

Title: A multimodal pipeline for quantifying speech and orofacial kinematic changes during deep brain stimulation in stroke patients

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Abstract: Deep brain stimulation (DBS) is increasingly explored as a therapeutic option for restoring motor function lost to stroke and other neurological conditions. However, fine-grained tools to quantify treatment-related changes in speech and orofacial movement remain limited. Clinical assessment of dysarthria and orofacial deficits is often perceptual and operator-dependent, limiting sensitivity to incremental change over a course of treatment. We developed and validated an open-source pipeline that characterizes acoustic-phonetic and facial-kinematic function, enabling quantitative comparison across DBS settings and over time. This work is primarily methodological and exploratory.The pipeline comprises two modules. The speech module ingests segmented audio and extracts a large set of metrics (e.g., intensity, fundamental frequency, formant structure, voice quality measures, articulation and pause timing, etc.) in a single pass; a pretrained phoneme-recognition model (*facebook/wav2vec2-lv-60-espeak-cv-ft*) then transcribes the produced phonemes and aligns them to the target utterance to compute phoneme-level accuracy and addition/substitution/deletion patterns. The facial module uses a landmark model (*MediaPipe Face Mesh*) placing 468 landmarks per frame, from which we derive several mouth-centric metrics (e.g., interlabial aperture, lip width, and asymmetry indices) normalized by inter-ocular distance to control for scale and head distance.
To assess rigor, we first validated outputs against extreme cases with known, clinically characterized deficits, confirming that derived metrics moved in the expected direction and magnitude before applying the pipeline to more subtle, stimulation-driven changes. We then applied it to 3 participants with post-stroke deficits (2 male and 1 female, 61 to 65 years old) undergoing DBS, recorded during standardized speech and facial motor tasks across DBS settings.The pipeline detected improvements over time and with stimulation ON compared to OFF: in both cases, speech improved in fluency, articulation rate, and phoneme-level accuracy, while facial kinematics showed increased lip aperture and excursion during both facial and speech tasks. These results demonstrate that a single, reproducible, open-source pipeline can capture quantitative markers of speech and orofacial change across stimulation settings and over time, offering an objective complement to perceptual assessment that could help guide DBS programming.

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Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.28/AA29

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UH3NS123135-01A1

Title: Spinal cord stimulation and intensive rehabilitation differentially alter reaching kinematics in people with post-stroke hemiparesis

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Abstract: Of the 800,000 new strokes in the US each year, over half lead to permanent upper limb deficits. Intensive rehabilitation is the primary intervention to improve function, but the demands of training are often not feasible and full motor restoration is rarely achieved. Cervical spinal cord stimulation (SCS) has emerged as a promising intervention, with our group showing immediate assistive and lasting therapeutic effects on strength and spasticity after 28 days of stimulation in a feasibility cohort (n=7), without formal rehab. Still, whether SCS and structured rehab improve function via similar or separate pathways remains unclear, a distinction with direct implications for the utility of SCS alone or potential synergy with physical therapy. Here, we report interim findings from an ongoing trial (STUDY25060125) evaluating preliminary long-term safety, feasibility, and efficacy of chronically implanted SCS in conjunction with physical training in individuals with post-stroke upper limb hemiparesis. Participants (n=2 to date) underwent 6 weeks of intensive upper limb training using the MindPod Dolphin (MindMaze) and Smart Glove (Neofect), followed by implantation of stimulating leads at the cervical level, 2 weeks of stimulator tuning, and a second 6-week phase of SCS combined with the same intense rehab protocol. 2D reaching performance was measured using the KINARM standard visually guided reaching task. After six weeks of rehab, Fugl-Meyer (FM) motor scores improved in both participants. Post-tuning, stimulation ON also improved FM score vs OFF. Strikingly, rehab had little effect on reach trajectory, while SCS tuning alone generated visible improvements in reach paths. Across kinematic features, PCA corroborated this pattern, with rehab shifting reaching trajectories away from unimpaired patterns vs SCS tuning moving them back toward unimpaired arm performance. An evaluation of the features driving this difference revealed that rehab led to slower but not more accurate trajectories. In contrast, SCS tuning post rehab reduced path length even with stimulation off. Additionally, while rehab had no effect on hand movement at the target, SCS tuning reduced end-point hand speed and target dwell-time path length, nearly completely ameliorating these at-target movements in one participant. Despite conserved effects of improving clinical scale motor score, these divergent kinematic signatures during reach may indicate that intensive rehab and SCS affect motor performance through different routes rather than a common pathway. Enrollment is ongoing, and the upcoming SCS + rehab phase will further clarify if these effects interact synergistically.

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receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro. **J.W. Krakauer:** None. **P. Gerszten:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro. **E. Pirondini:** None. **G.F. Wittenberg:** None. **M. Capogrosso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reach Neuro.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.29/AA30

Topic: F.05. Brain-Machine Interface

Support: R01 Grant NS131428
Wings for Life non-profit funding

Title: Development and characterization of NHP CST lesion model for enhancing rehabilitation efforts via pharmacological interventions

Authors: *C. JEZERC[1], A. DAMIANI[2], N. MACELLARI[2], Z. XU[3], L. LIANG[3], K. HOFFMANN[1], T. K. HITCHENS[4], J. A. GONZÁLEZ-MARTÍNEZ[5], M. CAPOGROSSO[5], E. PIRONDINI[3];
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Abstract: Corticospinal tract (CST) lesions, whether due to a stroke or spinal cord injury, interrupt long-range connections between cortical and spinal centers that regulate movements. While in most cases lesions are incomplete, surviving axons often lose their myelin sheath, leading to a dramatic decrease in their ability to efficiently conduct action potentials. We posit that promoting remyelination with pharmacological interventions may act synergistically with rehabilitation-focused therapies, thereby enhancing post-injury motor recovery.
In order to test this hypothesis, we developed a non-human primate (NHP) model of CST lesion, in which we thermocoagulate the CST fibers in the internal capsule (IC), where the descending tracts specific to hand and arm movement are located. By utilizing preoperative magnetic resonance imaging and computed tomography, we identified the stereotactic coordinates of the IC, which we then targeted surgically with a robotic approach previously developed in our lab. During surgery, we electrically stimulated the IC using a deep brain electrode to elicit motor evoked potentials across the finger, hand and arm muscles, confirming the accuracy of our target immediately prior to proceeding with the thermocoagulation. Following this IC lesion, the monkeys developed hallmark post-stroke motor symptoms, including mild to moderate loss of arm dexterity and severe loss of finger and hand control. To date, we performed this lesion in n = 6 animals and characterized their functional recovery with both cage-side assessment (n = 6) and with a battery of upper limb and hand dexterity tasks (n = 3) up to 4 months post lesion. Our

tasks allowed for kinematic and performance data analysis on gross strength and reaching capacity with the reach & pull and 3D reaching tasks as well as of grasp and finger dexterity via the box & blocks test and finger pinch (Brinkman board) task. Importantly, we can controllably induce different severity of lesions, as shown by different degrees of recovery correlated with the area of the IC we lesioned and characterized via post-mortem imaging and behavioral analysis. We believe that this model of CST lesion will constitute the ideal platform to investigate the effect of remyelination on functional recovery in primates.

Disclosures: C. Jezerc: None. **A. Damiani:** None. **N. Macellari:** None. **Z. Xu:** None. **L. Liang:** None. **K. Hoffmann:** None. **T.K. Hitchens:** None. **J.A. González-Martínez:** None. **M. Capogrosso:** None. **E. Pirondini:** None.

Poster

PSTR100: Neuroprosthetics: Control of Computer, Devices, and Body Parts I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR100.30/AA31

Topic: F.05. Brain-Machine Interface

Support: SnF mobility grant P500PT_225455

Title: Combined deep-brain and spinal cord stimulation for the recovery of hand dexterity after lesion of the cortico-spinal tract

Authors: *N. MACELLARI[1], A. DAMIANI[2], C. JEZERC[8], Z. XU[3], L. LIANG[3], K. HOFFMANN[4], C. GOSWAMI[1], S. BHATIA[5], P. GERSZTEN[6], J. A. GONZÁLEZ-MARTÍNEZ[5], M. CAPOGROSSO[5], E. PIRONDINI[7];
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Abstract: Dexterous hand control is essential for nearly every activity, yet even minor impairments can drastically affect quality of life. In humans and other primates, fine hand movements are mediated by the corticospinal tract (CST), an axonal pathway connecting cortical motor areas to the spinal circuits that control hand and finger muscles. A subset of CST axons forms direct monosynaptic connections onto the motoneurons controlling these muscles, forming a unique architecture that enables skilled, dexterous movement. Unfortunately, this same architecture makes primates particularly vulnerable to even minimal CST damage, which can result in permanent hand paralysis. Although physical therapy remains the standard of care, recovery of hand function is limited, underscoring the need for new therapeutic approaches. Our lab has previously shown that spinal cord stimulation (SCS) can be used to support residual CS connections to restore arm movements after stroke. However, SCS alone had minimal effects on hand functions and only in patients who retained either residual voluntary movement or motor

evoked potentials elicitable via transcranial magnetic stimulation, further highlighting the importance of residual CST signals. We therefore developed a synergistic approach that pairs SCS with motor thalamus deep-brain stimulation (DBS), a novel therapy designed to potentiate descending CST inputs. We tested this strategy in terminal experiments (n=5) and subsequently in chronically implanted NHPs (n=3) following a CST lesion. In terminal experiments, muscle activity was evoked through bursts of CST stimulation paired with DBS, SCS, or both across multiple frequencies. The combination of low-frequency DBS and SCS nearly doubled CST-evoked muscle activation. In the chronic cohort, 3 animals were trained on hand dexterity tasks prior to CST lesion, then assessed under four conditions: SCS alone, DBS alone, dual stimulation, or no stimulation. Across all animals, dual stimulation consistently produced the greatest improvements in hand dexterity. Together, these results demonstrate that combining DBS with SCS can significantly enhance hand muscle activation and restore hand function following CST injury, offering a promising therapeutic avenue for individuals with hand paralysis.

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Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.01/AA32

Topic: F.06. Posture and Gait

Support: Science committee of Armenia

Title: HYPOTHALAMIC CONTROL OF THE ACTIVITY OF VESTIBULAR NUCLEI NEURONS: ELECTROPHYSIOLOGICAL AND HISTOLOGICAL FEATURES

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Abstract: Abctract Background: Vestibulospinal neurons of the lateral vestibular nucleus (LVN) of Deiters' represents as a basic upper segmental center of regulation of the posture and locomotion. As respects to the afferent control of LVN neurons activity, it is of interest to study the mechanisms of vestibular-autonomic reflexes and particularly interrelations of LVN with hypothalamic neuroendocrine centers such as paraventricular (PVN) and supraoptic (SON) nuclei of hypothalamus . **Objective:** To understand the neuronal mechanisms of hypothalamic control of vesibular neurons we investigated effects the stimulation of hypothalaic PVN and SON nuclei. **Methods:** Animals were immobilized by 1% ditilin (25 mg/kg, i/p) and under artificial ventilation the section of spinal cord at T_1-T_3 level was realized to achieve preparation

encephale isole, i.e. Post stimulus activity was revealed as tetanic potentiation (TP) and depression (TD) following with post tetanic potentiation (PTP) and depression (PTD) of different latency, intensity and duration. For histochemical investigation parts of the brain stem were fixed for 2-3 days in 5% neutral formalin prepared on phosphate buffer. The frontal frozen sections (40-50 μM) were processed by help of new approach of revealing the activity of Ca^{2+}-dependent acidic phosphate. In separate experiment using HRP method of retrograde transport the connections of PVN and SON with LVN were studied. **Results:** Results indicate on presence of excitatory and inhibitory post stimulus development of LVN neurons activity to stimulation of PVN and SON with different sequence, intensity, duration and latency of onset. Importance of providing the mentioned depression by higher brain endocrine centers, such as PVN is expected by permanent necessity not only the control of LVN activity realized through brain motor centers when their activity predominance may accrue upset of motor flexor-extensor balance, but also the autonomic displacements following the possible intensification of vestibular tonus. Moreover, existence of excitatory reaction indicates to delicate regulatory influence of PVN and SON on the vestibular complex. Earlier in a series of intracellular experiments (V.H.Sarkisian, 2000)has been shown that stimulation of numerous brain structures (cerebellum, spinal trigeminal nucleus, lateral reticular nucleus, inferior olive, posterior hypothalamus and etc.) evoked IPSP in Deiters' neurons. **Conclusion:** Relationships of the hypothalamus with vestibular neurons provides not only an integrative network for regulation of posture and orientation in space, but also involves in the central regulation of autonomic functions.

Disclosures: N. Behnam Dehkordi: None. **V. Sarkisian:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR101.02/BB1

Topic: F.06. Posture and Gait

Support: VIEP-BUAP grant to Cuerpo Académico en Neuroendocrinología (BUAP-CA-288)

Title: Systemic administration of pramipexole and 4-aminopyridine improve the gait pattern in male taiep rats: a model of human leukodystrophy

Authors: *J. R. EGUIBAR[1], C. CORTES[2], A. UGARTE[3], R. CASTILLO[4], D. A. QUINTERO-PRADO, Sr.[5];
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Abstract: Systemic administration of pramipexole and 4-aminopyridine improve the gaitpattern in male *taiep* rats: a model of human leukodystrophy.The *taiep* rats are a well stablished model of tubulinopathy with a point mutation inthe tubulin β 4A gene associated with hypomyelination followed by a progressivedemyelination in the central nervous system. *Taiep* rats is the only available modelof human leukodystrophy named hypomyelination with atrophy of the basal gangliaand cerebellum (H-ABC). The aim of this study was to evaluate the effects ofconcomitant systemic administration of a D2-like dopaminergic agonist pramipexoleplus 4-aminopyridine (4-AP), a well-known voltage-gated potassium channel blockeron the gait pattern in adult male taiep rats.The subjects were maintained under standard conditions and following ethicalMexican and international legislations including ARRIVE 2.0 guidelines. All subjectswere recorded in control conditions after intraperitoneal injection physiological salinesolution or after injection of 1 mg/Kg of pramipexole followed by 4-AP with threedifferent doses 1, 1.5 or 2 mg/Kg. The gait patterns were recorded using CatWalk™system (Noldus Technologies, The Netherlands). We measured during gait patternacross CatWalk apparatus the following parameters: support base, speed, stridelength, and regularity index among the extremities and step sequences. Systemicadministration of pramipexole plus 4-aminopyridine with 1 or 1.5 mg/Kg dosesinduced similar changes as when the drugs were administered independently.However, when we injected pramipexole plus 2 mg/Kg 4-AP induced a significantincrease in the support base ($P \leq 0.05$), a reduction of stride length ($P \leq 0.05$), whichinduced a reduction on the stepping velocity ($P \leq 0.05$), and a decrement in the gaitregularity index ($P \leq 0.05$). These changes in gait parameters enhance forwardlocomotion and reduced ataxia in male *taiep* subjects. In base of our results, weconsider that dopaminergic D2 agonist improve gait pattern and 4-AP must improvethe transmission of action potentials at spinal central pattern generator and in thecontrol locomotor mechanism in the brainstem in this tubulinopathy rat model thatimprove gait pattern and could be useful for treatment in leukodystrophies.

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Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.03/BB2

Topic: F.06. Posture and Gait

Support: R01NS110853

Title: Heterozygous blockade of torsinA ATP hydrolysis causes latent motor dysfunction

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Abstract: DYT-TOR1A dystonia is a dominantly inherited neurodevelopmental movement disorder caused by a deletion of glutamic acid in the TOR1A gene that impairs torsinA function. Heterozygous *Tor1a*$^{\Delta E/+}$ knock-in mice do not have overt abnormal behavioral or histopathological phenotypes, while homozygous *Tor1a*$^{\Delta E/\Delta E}$ mutant mice die on the day of birth and display neuron-specific nuclear membrane abnormalities. A conserved glutamic acid at residue 171 is essential for activating ATP hydrolysis. When mutated to glutamine, torsinA can bind, but not hydrolyze ATP, therefore TOR1A^{E171Q} is an ATPase-deficient torsinA mutation that impairs ATP hydrolysis and reduces torsinA function. Homozygous *Tor1a*$^{EQ/EQ}$ mutants exhibited severe neonatal lethality, with all pups dying within 72 h. In contrast, heterozygous mutants survived normally. *Tor1a*$^{EQ/EQ}$ mice exhibited nuclear blebs in striatum, cortex and brain stem, but the NE was normal in *Tor1a*$^{EQ/+}$ mice. Motor behaviors were assessed using the tail suspension test, screening for limb clasping or twisting behavior. *Tor1a*$^{EQ/+}$ mice showed no significant clasping behavior at P21 or P56 when assessed in a single session. However, daily testing over five consecutive days caused progressive worsening of clasping at P21 and P90, suggesting that repeated motor challenge unmasks motor dysfunction not apparent under standard single-session conditions. Motor behavior was also assessed using an observer-free chamber designed to capture fine movements from below (BlackBox One) and analyzed using DeepLabCut's pose estimation and Motion Sequencing (MoSeq) to quantify movement kinematics and behavioral syllable structure. DeepLabCut displayed subtle axial motor abnormalities and altered forelimb positioning in heterozygotes without significant changes in overall locomotor activity. MoSeq identified 13 dominant behavioral syllable trajectories, with heterozygotes exhibiting increased duration of a syllable associated with crouched turning behavior and increased frequency of a forward-progression locomotor syllable. These findings are consistent with torsinA loss of function causing motor abnormalities and demonstrate that *Tor1a*$^{EQ/+}$ mice exhibit subtle motor abnormalities not readily detected by conventional behavioral assays. High resolution phenotyping and repeated motor challenges may provide sensitive tools for detecting and characterizing motor dysfunction in DYT-TOR1A and other forms of dystonia.

Disclosures: D. Gupta: None. **G. Gent:** None. **N. Liggans:** None. **S. Pappas:** None. **W.T. Dauer:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.04/BB3

Topic: F.06. Posture and Gait

Support: NIH NS132487

Title: V3 Neurons Mediate Standing and Leaping Movements

Authors: *T. AYANTAYO[1], M. ALMOKDAD[2], K. HARI[2], K. K. FENRICH[3], D. J. BENNETT[2];
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Abstract: V3 neurons are Sim1-expressing glutamatergic spinal interneurons with predominantly commissural axonal projections and extensive propriospinal connectivity. They contribute approximately 20% of the excitatory interneuron drive to motoneurons and provide equal innervation to flexor and extensor motoneuron pools. In addition, they receive proprioceptive, reticulospinal, and vestibulospinal inputs, suggesting a role in postural control. Here, we investigate the role of V3 neurons in standing and their capacity to mediate postural recovery following spinal cord injury (SCI). Optogenetic activation of V3 neurons in Sim1//Chr2 mice evoked prolonged excitatory postsynaptic potentials (100 ms) in vitro that were preserved following chronic SCI. In awake mice, a 10 Hz light train delivered through an LED window implant over the L2 spinal cord produced rapid (≤50 ms) and sustained weight-bearing standing responses. During locomotion, V3 activation overrode ongoing locomotor central pattern generator (CPG) output, imposing bilateral limb alignment and robust hindlimb extension(standing). Interestingly, standing in staggered hemi-section (T8 and T10) mice were comparable to intact animals following optogenetic activation. To determine whether V3 neurons contribute to physiologic standing, we developed an assay using brief (1 ms) bilateral hind paw stimulation. This assay elicited standing with peak trunk height and latency comparable to those induced by optogenetic V3 activation. However, following paw stimulation, V3OFF mice (Sim1//flx-VGlut2) achieved only about 50% of peak standing height and exhibited double the latency to peak standing relative to wild-type (WT) mice ($p<0.05$). When we combined subthreshold sensory and optogenetic stimulation, supra-linear extensor responses were observed, suggesting convergent recruitment of a similar excitatory pathway. Acute chemogenetic silencing of V3 neurons in Sim1//DREADDi with the DREADD ligand JHU37160 reduced walking trunk height by 50%, abolished extensor responses during standing and leaping following bilateral hind paw stimulation. In addition, the difference between the peak trunk height and foot height was reduced by about 75% when compared to pre-drug measurements ($p<0.05$), indicating increased foot flexion. Collectively, these findings identify V3 neurons as a propriospinal excitatory network that rapidly recruits extensor motor output to generate standing, bypassing and constraining locomotor CPG activity. Targeting V3 circuitry may therefore represent a promising approach for restoring standing function after SCI.

Disclosures: T. Ayantayo: None. **M. Almokdad:** None. **K. Hari:** None. **K.K. Fenrich:** None. **D.J. Bennett:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.05/BB4

Topic: F.06. Posture and Gait

Support: (NSF) DBI 2015317

Title: Bayesian Tuning of a Mammalian Motor Circuit Enables Robust Locomotion Across Control Regimes

Authors: *C. B. JACKSON[1], R. D. QUINN[2];
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Abstract: Mammalian locomotion is traditionally attributed to descending commands to motor neurons from central pattern generators (CPGs). However, recent studies suggest that at low speeds, motor circuits can produce rhythmic motion through sensory feedback alone, without CPG input. In this work, we develop a computational model of a motor circuit composed of motor neurons, Ia inhibitory interneurons, and Renshaw cells, modeled using a non-spiking leaky integrator neural model. We first tune the motor circuit controlling the hip joint in the sagittal plane using a simplified rat hindlimb model performing airstepping. The neural model is tuned using a Markov Chain Monte Carlo (MCMC) parameter search in a Bayesian inference framework to produce stable, rhythmic oscillations in the absence of CPG input. These results are then grouped using K-means clustering to identify distinct functional regimes. We then extend the neural model by adding rhythmic input from CPG's using a two-layer CPG network architecture to control the hip, knee, and ankle joints in both hindlimbs during walking with ground contact. We perform a perturbation analysis by applying a torque the hip at various phases in the gait cycle and evaluating the system's ability to recover. Initial results reveal a relationship between cluster dispersion and perturbation response: moderately dense clusters show greater robustness, while overly concentrated or sparse clusters result in degraded performance. This suggests that robustness arises not from precise tuning, but from flexibility. Motor circuits operating within broad regions of parameter space can maintain stability across varying operating regimes, from sensory-driven to CPG-modulated control.

Disclosures: C.B. Jackson: None. **R.D. Quinn:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.06/BB5

Topic: F.06. Posture and Gait

Support: N62909-24-1-2015

Title: Systematic mapping of locomotor responses evoked by brain microstimulation in goldfish

Authors: *A. LAZAROVICH[1], D. ZLOTNIKOV[1], R. SEGEV[2], O. BEN-SHAHAR[1];
[1]The Stein Fac. of Computer and Information Sci., Ben-Gurion Univ. of the Negev, Beer Sheva, Israel; [2]Dept. of Life Sci., Ben Gurion Univ. of the Negev, Beer Sheva, Israel

Abstract: The vertebrate brain steers whole-body locomotion through command signals descending from the brain to the spinal cord, yet the sites where localized electrical input reliably biases the vigor and pattern of movement remain mostly unmapped, especially in swimming vertebrates. Identifying such sites matters both for understanding how midbrain and brainstem circuits organize locomotion and for biohybrid systems that aim to affect an animal's behavior through targeted neural input. Prior work indicates that the nucleus of the medial longitudinal fascicle (NFLM), a midbrain structure beneath the optic tectum, lies along the descending pathways that shape swimming and turning in teleost fish, making it a strong candidate site at which stimulation produces graded motor output. Here we study the effects of external stimulation to that region and map its parameters to motor output to eventually characterize the swimming evoked by intracerebral electrical microstimulation in head-fixed adult goldfish (Carassius auratus). Toward that end, we advanced along a dorsoventral midbrain track passing through the NFLM and stimulated at a range of electrode positions and current amplitudes through a wireless microstimulator. An automatic image processing, pose-tracking pipeline measured the evoked tail-beat kinematics and body-bend angle and separated stimulus-locked movement from spontaneous activity. From these measurements we map how depth and current set the magnitude, latency, and pattern of evoked locomotion, constructing individual-specific dose-response mapping and localizing the positions at which stimulation most reliably drives desired movement. By resolving where along the track one obtains repeatable, amplitude-dependent swimming emerges, the work links the functional organization of the fish midbrain to controllable, parameter-tuned locomotor output.

Disclosures: A. Lazarovich: None. **D. Zlotnikov:** None. **R. Segev:** None. **O. Ben-Shahar:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.07/BB6

Topic: F.06. Posture and Gait

Support: NINDS Grant 1ZIANS003153-03

Title: A shortcut spinal circuit for nociceptive limb withdrawal reflex in mice

Authors: *P. MEKDARA[1], A. LEVINE[2];
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Abstract: Potential harmful stimuli are detected at the skin where cutaneous nociceptive sensory neurons activate spinal reflex mechanisms to drive a withdrawal of an affected limb away from the potential harmful source. While the spinal cord plays a key role in this behavior, the intraspinal mechanisms that underlie the sensorimotor integration and the resultant motor

programs that are produced to coordinate muscle firing patterns have yet to be understood. Using optogenetics and multi-electrode array electrophysiology in awake behaving mice, we investigate the neural mechanisms that underlie the patterns of neural activity in the lumbar spinal cord during a stimulus-driven hindlimb withdrawal reflex. Here, we first established methods for high-density *in vivo* electrophysiology recordings from single units in the spinal cords of vertebrally-fixed, awake, and behaving mice. Mice in this preparation can produce clear, repeatable behaviors including self-driven locomotion, grooming, optogenetically-cued limb withdrawal reflexes, and clear responses to different naturalistic stimulations of the hindlimb receptive field. Next, we characterized single unit neural firing parameters across multiple animals as a function of laminar distribution across the full dorsal-ventral axis of the spinal cord. We found that neurons in the medial deep dorsal horn and ventral horn regions had short latency responses and high firing rates following nociceptive stimulation to the paw. Therefore, we hypothesize that (1) activity from a hindlimb withdrawal response in the ventral horn will be strongly correlated with early activity in the deep dorsal horn and (2) that perturbing specific interneuron populations optogenetically in this region will allow us to investigate the function of those interneurons involved in hindlimb withdrawal reflexes; thereby, identifying a shortcut spinal circuit for ultra-fast reflexes.

Disclosures: P. Mekdara: None. **A. Levine:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.08/BB7

Topic: F.06. Posture and Gait

Support: NIH R01HD088417

Title: Fear of Movement and Pain Catastrophizing Are Associated with Increased Postural Variability

Authors: *S. M. VAN DER VEEN[1], J. S. THOMAS[2];
[1]Physical Therapy, East Carolina Univ., Greenville, NC; [2]Virginia Commonwealth Univ., Richmond, VA

Abstract: Abstract: Fear-related psychological factors are thought to influence movement behavior in individuals with pain, yet their effects on movement outcomes versus control strategies remain unclear. Prior work suggests that pain catastrophizing is associated with altered movement strategies rather than simple mechanical limitation. This study examined relationships between fear of movement (Tampa Scale of Kinesiophobia; TSK), pain catastrophizing (Pain Catastrophizing Scale; PCS), limb loading, and postural control during a virtual reality reaching task.Participants (n = 103; 65 female; age = 40.2 ± 13.1 years) reached toward visually presented targets while standing. The task required controlled weight shifting and load transfer toward the

reaching limb, enabling simultaneous quantification of limb loading and center of pressure (COP) dynamics. COP measures included anterior-posterior variability (COP_AP), medial-lateral variability (COP_ML), and total COP path length (COP_PATH). TSK scores ranged from 35-60 and PCS scores ranged from 0-48.PCS was associated with lower limb loading ($r = -0.24$, $p = 0.018$), whereas the association with TSK did not reach significance ($r = -0.19$, $p = 0.070$). In contrast, both TSK and PCS were positively associated with COP path length (TSK: $r = 0.28$, $p = 0.006$; PCS: $r = 0.27$, $p = 0.008$), indicating greater postural variability during reaching. Neither TSK nor PCS was associated with COP_AP or COP_ML.These findings indicate that fear of movement and pain catastrophizing have limited effects on gross movement outcomes such as limb loading, but more pronounced effects on movement control. Increased COP path length with greater fear-related cognitions may reflect altered motor adaptability and sensorimotor integration, suggesting these individuals complete the task using different coordination strategies despite relatively preserved task performance. This interpretation is consistent with prior work demonstrating that changes in movement variability accompany impaired coordination and reduced adaptability following injury, as well as altered movement strategies in low back pain. The dissociation between relatively preserved movement output and altered postural control supports a model in which psychological factors influence coordination and stability more strongly than task execution, suggesting that fear-avoidance is expressed through altered movement variability rather than reduced performance.

Disclosures: S.M. Van Der Veen: None. **J.S. Thomas:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.09/BB8

Topic: F.06. Posture and Gait

Title: Task-dependent synergism between the soleus and tibialis anterior during standing postural control

Authors: *M. ZABACK[1,2], C. K. THOMPSON[2];
[1]Hlth. and Rehabil. Sci., Temple Univ., Baltimore, MD; [2]Hlth. and Rehabil. Sci., Temple Univ., Philadelphia, PA

Abstract: The neural drive to motor pools is typically organized such that the muscles contributing to the intended movement are activated, while those opposing it are suppressed. However, the mechanical relationships between muscles can vary with biomechanical task constraints resulting in a need to modify the neural drive to motor pools accordingly. Here, we investigate how neural drive to the soleus (SOL) and tibialis anterior (TA) is adjusted to accommodate changes in biomechanical constraints during postural tasks. Nine healthy young adults performed trials of dual- and single-legged standing on a force plate while high-density surface EMG was recorded from the right SOL and TA. Directional tuning curves for each

muscle were constructed by calculating the magnitude of EMG preceding COP peaks oriented in different directions across the transverse plane. During dual-legged standing, both muscles tuned their activity uniformly along the sagittal plane but in opposite directions, indicative of an antagonist relationship. When standing on one leg, tuning curves for both muscles rotated significantly laterally and were overlapping, indicative of a synergistic relationship. These changes in directional tuning were accompanied by changes in estimates of shared neural drive, with intermuscular coherence absent during dual-legged standing, but highly significant during single-legged standing. Analyses of time-dependent intermuscular coherence revealed that the magnitude of shared neural drive was further adjusted depending on the direction of COP movement, with coherence increasing significantly prior to laterally-directed COP peaks during single-legged standing. Collectively, these observations reveal a sophisticated level of neural control, whereby the postural control system dynamically adjusts neural drive to lower limb motor pools in real time depending on biomechanical task constraints in order to maintain equilibrium.

Disclosures: M. Zaback: None. **C.K. Thompson:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.10/BB9

Topic: F.06. Posture and Gait

Support: Natural Sciences and Engineering Research Council of Canada
Ontario Graduate Scholarship Program

Title: Feasibility of simultaneous EEG, fNIRS, and sEMG data acquisition during internal perturbations

Authors: *T. A. GREEN[1,2,3,4], I. TAIT[1,2,3,4], S. PETERS[1,2,3,4];
[1]Univ. of Western Ontario, London, ON, Canada; [2]Parkwood Inst., London, ON, Canada; [3]Gray Ctr. for Mobility and Activity, London, ON, Canada; [4]Lawson Res. Inst., London, ON, Canada

Abstract: Background: Maintenance of posture relies on coordinated interactions between cortical motor regions and peripheral musculature. Characterization of these interactions has largely relied on a uni-modal approach, limiting the understanding of the spatiotemporal dynamics underlying motor control. Electroencephalography (EEG) provides excellent temporal resolution but limited spatial specificity, whereas functional near infrared spectroscopy (fNIRS) offers improved spatial localization but limited temporal resolution. Consequently, a uni-modal neuroimaging approach overlooks important aspects of motor network function. Simultaneous EEG-fNIRS data acquisition may provide a comprehensive analysis of cortical spatiotemporal activity, while concurrent sEMG examines the muscular output associated with these cortical processes and provides a foundation for future investigations of corticomuscular coupling.

Methods: One adult female (24 years) completed two internal perturbation tasks: a rapid shoulder flexion and a unilateral step while simultaneous EEG, fNIRS, and sEMG was collected. Neuroimaging consisted of 20 EEG channels and a 16-source, 15-detector fNIRS configuration positioned over cortical motor regions. sEMG was recorded from the bilateral biceps femorum and medial gastrocnemii. Data synchronization was achieved using TTL pulses. Modality-specific pipelines were used to extract movement-related cortical potentials, hemodynamic responses, and muscle activation. Feasibility was evaluated using signal-to-noise ratio (SNR) for EEG and sEMG and coefficient of variation (CV) for fNIRS. Neuroimaging data integrity was evaluated based on channel retention following pre-processing. **Results:** Mean EEG SNR for all channels was 5.06 dB. Mean fNIRS CV was 3.85 and 3.35 for HbO and HbR respectively. Following preprocessing, 20 of 20 EEG channels and 56 of 58 fNIRS channels were retained for analysis, corresponding to channel retention rates of 100% and 97%, respectively. Lastly, mean sEMG SNR was 20.07 dB for the four muscles. **Discussion:** Preliminary results demonstrate that a multimodal approach during internal perturbations can yield EEG, fNIRS, and sEMG data with acceptable signal quality and can retain high neuroimaging channels. These findings support the feasibility of simultaneous multimodal acquisition during functional movement tasks and provide a foundation for future investigations of cortical motor network dynamics. By integrating complementary temporal, spatial, and muscular information, this approach may improve understanding of the neural mechanisms underlying movement and postural control.

Disclosures: T.A. Green: None. **I. Tait:** None. **S. Peters:** A. Employment/Salary (full or part-time):; University of Western Ontario.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.11/BB10

Topic: F.06. Posture and Gait

Support: UIC AHS EXITO Pilot Award

Title: Cortical Activity During Overground Turning Scales With Turn Angle: A Mobile EEG Study

Authors: *C. KUESTER, J. SUN, D. SAMSON, C. LIU;
Univ. of Illinois Chicago, Chicago, IL

Abstract: Daily walking requires frequent direction changes, and turning steps are over a third of all steps. Turning raises fall risk in older adults, and a fall during a turn is roughly eight times more likely to cause a hip fracture than during straight walking. Turn angle modulates ground reaction forces, step strategy, and turn duration, signaling greater motor control demand at larger angles, yet the cortical control of overground turning remains poorly understood. Mobile electroencephalography (EEG) records cortical activity during real walking and, with

independent component analysis (ICA), resolves it at the source level. Mobile EEG of level walking and obstacle crossing has implicated motor, frontal, cingulate, and posterior parietal cortices. Whether these sources engage during overground turning, and whether engagement scales with turn amplitude, is unknown. Fourteen young, healthy adults (seven female, seven male; ages 18 to 31) walked an instrumented path with non-dominant turns at 90, 120, and 180°, interleaved with straight walking, 42 trials per condition. We recorded high-density EEG with noise and neck electromyography (EMG) references, and iCanClean removed noise and muscle artifact. Trials were epoched to the turn and time-warped to the gait cycle. We retained brain-classified independent components (ICs; ICLabel brain ≥ 50%, residual variance ≤ 15%, negative spectral slope), clustered them across subjects and mapped them to an anatomical atlas. We computed event-related spectral perturbations (ERSP) per component across the warped cycle. In this preliminary cohort, clusters localized to frontal, sensorimotor, cingulate, and occipital cortex. In medial frontal, and mid-cingulate clusters, theta to beta power increased after right toe-off and scaled with turn amplitude, strongest at 180°. These findings show source-resolved mobile EEG of overground turning is feasible and lays the groundwork for testing cortical correlates of turn-related fall risk in older and clinical groups.

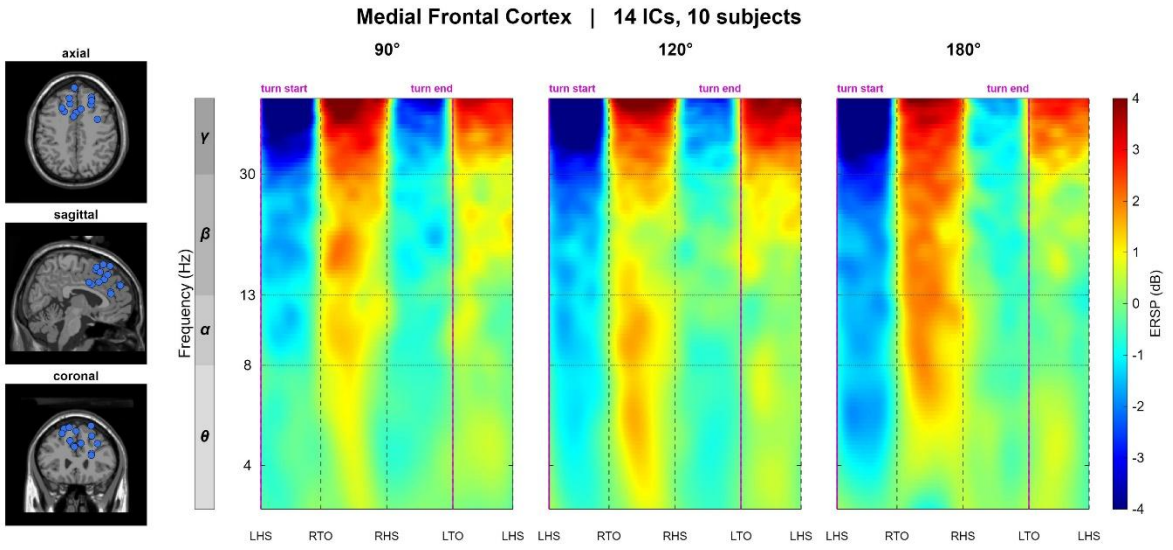


Figure 1. Medial frontal cluster (14 ICs from 10 subjects). Left: dipole locations on axial, sagittal, and coronal slices of the Montreal Neurological Institute (MNI) template brain. Right: cluster-mean ERSP across one turn stride at 90, 120, and 180°, time-warped to the gait cycle with events at left heel strike (LHS), right toe-off (RTO), right heel strike (RHS), and left toe-off (LTO). Magenta lines mark the turn-initiating step, from turn start (LHS) to turn end (LTO). Color: power change in dB from the mean across the turn cycle; warm increase, cool decrease. 3 to 50 Hz.

Disclosures: C. Kuester: None. **J. Sun:** None. **D. Samson:** None. **C. Liu:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.12/BB11

Topic: F.06. Posture and Gait

Title: Coupling among gait, respiration, and neural oscillations during self-initiated locomotion

Authors: E. NEUBERG[1,2], K. DEHDAR[1,2], ***B.-M. GU**[1,2,3];
[1]Ctr. for Discovery and Innovation, Hackensack Meridian Hlth., Nutley, NJ; [2]Neurosci. Inst., Hackensack Meridian JFK Univ. Med. Ctr., Edison, NJ; [3]Neurol., Hackensack Meridian Sch. of Med., Nutley, NJ

Abstract: Locomotion is a fundamental behavior that requires coordination of multiple systems. This coordination includes the diaphragm to adjust breathing to meet metabolic demands and improve respiration efficiency. Rhythmic interactions between locomotion and respiration, known as locomotor-respiratory coupling (LRC), have been observed across a wide range of species. However, the neural correlates of this coupled behavior remain poorly understood. Growing evidence suggests that neural oscillations across multiple brain regions are coupled to respiratory rhythms. Here, we focused on the coupling of neural oscillations in the substantia nigra pars reticulata (SNr) and primary motor cortex (M1) with respiration and gaiting rhythms, as both regions play critical roles in movement control. In particular, the SNr, a major basal ganglia output nucleus, is well positioned to coordinate gait and respiration because it projects directly to the mesencephalic locomotor region and has recently been shown to regulate breathing rates. To investigate these interactions, we measured local field potentials (LFPs) from the SNr and M1 during self-initiated locomotion. Mice were head-fixed on a treadmill and trained over multiple days. Respiration was recorded using diaphragm electromyography (EMG) and gait behavior was measured using piezoelectric sensors placed beneath on treadmill. We analyzed the relationships among gait, respiration, and neural rhythms in the SNr and M1. To quantify cross-frequency coupling, we calculated the modulation index (MI) between the amplitude of neural oscillations and the phase of either respiration or gait rhythms. We found that SNr beta (15-30Hz) and low gamma (30-50Hz) oscillations were significantly coupled to both gait and respiratory rhythms. Interestingly, SNr beta and low gamma rhythms were preferentially coupled to distinct phases of respiratory cycle, whereas both frequency bands were coupled to similar phases of the gait cycle. These findings demonstrate systematic coupling between neural oscillations and the rhythms of respiration and locomotion, highlighting the importance of coordinated brain-body dynamics during voluntary locomotive behaviors. Furthermore, these findings suggest significant implications for understanding Parkinson's disease, which is characterized by elevated beta rhythms and gait dysfunction, including freezing of gait.

Disclosures: E. Neuberg: None. **K. Dehdar:** None. **B. Gu:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.13/BB12

Topic: F.06. Posture and Gait

Title: Human Electrical Brain and Muscle Dynamics During Overground Walking and Stepping Over Obstacles

Authors: *M. MUSTANSIR, A. D. NORDIN;
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Abstract: Walking in the real world requires visuomotor integration and precise step planning to avoid trips and falls. The effects of gait speed on electrocortical spectral power dynamics have been studied during treadmill locomotion using mobile electroencephalography (EEG). Spectral power increases from cortical structures involved in visuomotor processing during obstacle navigation have been identified, but communication between the brain and lower-limb muscles during visually guided overground walking remains unclear. We recorded electrical brain and muscle dynamics (1) during unobstructed overground walking and (2) while visually tracking and stepping over obstacles in the environment, at two walking speeds. We hypothesized that sensorimotor alpha (8-13Hz) and beta (13-30Hz) band spectral power would decrease during forward limb swing, along with increased corticomuscular connectivity from sensorimotor cortex to lower limb muscles due to feedforward control. We further hypothesized that sensorimotor alpha and beta band spectral power would increase during double limb support, with greater corticomuscular connectivity from lower limb muscles to sensorimotor cortex due to sensory feedback. During step planning while approaching obstacles in the environment, we anticipated reduced occipitoparietal alpha and beta band power, followed by increased theta (4-8Hz) and alpha band spectral power from supplementary motor, premotor, and parietal immediately before stepping over the obstacles. We anticipated that visuomotor planning would increase sensorimotor corticomuscular connectivity to the hip flexor and ankle dorsiflexor muscles during step modifications. Participants were instrumented with a 64-channel mobile EEG to record electrical brain activity, bilateral 16-channel lower limb electromyography (EMG) to record muscle activations (biceps femoris, rectus femoris, vastus lateralis, vastus medialis, tibialis anterior, gastrocnemius medialis and lateralis, and soleus muscles), seven inertial measurement units to capture lower body kinematics, and eye-tracking glasses to record gaze behavior. We decomposed the EEG into independent cortical sources fitted to brain anatomy, and calculated corticomuscular connectivity with synchronized EMG. By studying healthy neural dynamics during visual tracking and stepping over obstacles, we identified locomotor network activity that may be compromised due to aging or neurological disorders, informing targeted neurorehabilitation strategies.

Disclosures: M. Mustansir: None. **A.D. Nordin:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.14/Web Only

Topic: A.07. Development of Neural Systems

Title: Developmental changes in rectus femoris activation patterns during knee flexion-extension movements in supported standing in infants

Authors: *T. NAKAMURA[1], K. FUJIWARA[2], T. KIYOTA[2], A. NAKAMURA[3], M. IREI[3];
[1]Osaka Child Welfare Col., Osaka-shi / Osaka, Japan; [2]Kanazawa Gakuin Univ., Kanazawa, Japan; [3]Osaka Hlth. Sci. Univ., Osaka, Japan

Abstract: We investigated developmental changes in the muscle activation patterns of the rectus femoris (RF) during knee flexion-extension movements performed by infants during supported standing. Participants comprised 7 healthy infants and 11 healthy adults. Each infant participated in measurements every 2-3 weeks from the supported standing (SS) stage through the independent standing (IS) stage to the period just prior to the onset of independent walking (IW onset). Infants performed both single and repetitive knee flexion-extension movements in these stages. Muscle activation patterns of RF were analyzed in terms of the time from activation onset to peak (RF peak latency) and the time from peak to 34% of peak amplitude (RF decay time). In addition, RF activity during the patellar tendon reflex was recorded, and the same parameters were analyzed. A single knee flexion-extension movement was observed during the SS stage. Its frequency decreased during the IS stage, and the movement was no longer observed during the period just prior to IW onset. The RF activation pattern during single knee flexion-extension was similar to the pattern during the patellar tendon reflex. In repetitive knee flexion-extension movements, the RF peak latency and RF decay time became longer after the IS stage than during the SS stage. These activation times were shorter in infants than in adults. These results suggest that developmental changes in RF activation patterns during knee flexion-extension reflect a transition from reflex-like activity to more voluntary activity.

Disclosures: T. Nakamura: None. **K. Fujiwara:** None. **T. Kiyota:** None. **A. Nakamura:** None. **M. Irei:** None.

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.15/BB13

Topic: F.06. Posture and Gait

Title: Reflexive somatosensory feedback contributes to online movement correction in the absence of muscle stretch

Authors: *S. ITO, N. ABEKAWA;
NTT Communication Sci. Labs., Atsugi, Japan

Abstract: Stable motor execution is supported by multiple feedback control mechanisms, among which rapid somatosensory feedback plays a critical role. A well-known example is the stretch reflex. Because muscle spindle activity is primarily generated by muscle stretch, stretch reflexes have been considered to compensate for postural errors involving muscle lengthening. However, daily movement errors do not necessarily involve muscle stretch, as when lifting luggage that is heavier than expected. Although rapid feedback responses of the upper limb have been extensively studied using stretch-evoked perturbations, it remains unclear whether comparable responses occur when movement errors arise without muscle stretch. Here, we examined whether reflexive somatosensory feedback contributes to online movement correction when reaching is opposed by a resistive force without muscle stretch. Participants performed horizontal reaching movements toward a visual target while grasping a robotic manipulandum. In 25% of randomly selected trials, a mechanical perturbation was applied at the movement midpoint in the direction opposite to the ongoing movement. The perturbation was a velocity-dependent force applied for 100 ms (gain: d = -30 N·s/m), which rapidly decelerated the hand but never reversed its velocity. Thus, the external force did not induce muscle stretch. In response to this deceleration, participants rapidly re-accelerated the hand toward the target. Pectoralis major EMG, recorded from the agonist muscle for the reach, showed a clear increase approximately 50 ms after perturbation onset. Thus, muscle activity comparable to a long-latency stretch reflex was observed even though the pectoralis major was not stretched. In a separate block, participants were instructed to correct their movement backward, rather than toward the target, when they detected the perturbation. Even then, pectoralis major activity was observed approximately 50 ms after perturbation onset. In contrast, posterior deltoid activity, associated with the instructed backward correction, emerged only after 100 ms, suggesting a voluntary response. Together, these results show the involuntary nature of the rapid response and suggest that it may be generated selectively when it acts to compensate for deviations from the planned movement. These findings indicate that reflexive somatosensory feedback responses can emerge when resistive forces interfere with ongoing movement, even without muscle stretch, and can help reduce movement error, suggesting a broader role in online motor correction than previously recognized.

Disclosures: S. Ito: A. Employment/Salary (full or part-time):; NTT, Inc. **N. Abekawa:** A. Employment/Salary (full or part-time):; NTT, Inc..

Poster

PSTR101: Posture and Gait: Low-Level to Higher-Order Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR101.16/BB14

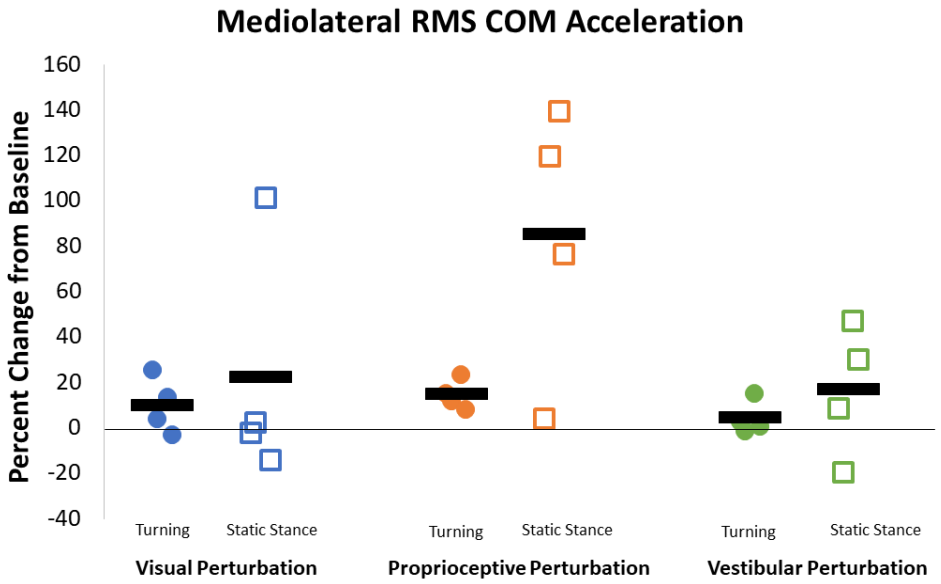
Topic: F.06. Posture and Gait

Support: CCTR Endowment Fund of Virginia Commonwealth University and the Wright Center for Clinical and Translational Research

Title: Sensory reliance during 360 degree turns versus quiet stance

Authors: *C. DUPPEN, K. SHAAB, A. FLACH;
Physical Therapy, Virginia Commonwealth Univ., Richmond, VA

Abstract: Falls during turns are 8 times more likely to result in a hip fracture than falls during straight path walking. While sensory reliance during quiet stance is well-studied, it remains unclear if a similar pattern applies to turning. This limits the design of targeted interventions to improve turning and reduce fall risk. The purpose of this work was to determine if sensory reliance during 360° turns mirrors that of quiet stance. We hypothesized vestibular input would carry greater relative importance during turning due to increased semicircular canal activation. To test this, 4 young adults (18-35 years) completed quiet stance and 360° turns under altered sensory conditions using a crossover design. We perturbed vision via prism glasses, proprioception via compliant foam, and vestibular input via pulsed monopolar galvanic vestibular stimulation. The primary outcome was mediolateral root mean square center of mass acceleration (ML COMacc), normalized to turn velocity during turns, and quantified as percent change from baseline. Due to our small sample size, no statistical analyses were performed. Qualitatively we noted a task dependent shift in sensory reliance (Figure 1). During quiet stance, proprioceptive disruption induced a large increase in ML COMacc (Mean: 85%; Range [4%, 139%]), while visual (22%; [-14%, 101%]), and vestibular (17%; [-19%, 47%]) perturbations had modest effects. During turning, the effects of all three perturbations were attenuated, and the difference between proprioceptive and visual disruption narrowed to 5% (proprioceptive: 15%, [8%, 23%]; visual: 10%, [-3%, 25%]; vestibular: 4%, [-1%, 15%]). Because equipment and sample size limitations prevented determining the gain of our perturbations, only general patterns can be compared, and the variance in our cohort limits interpretations. However, our findings suggest young adults employ a task-dependent strategy, where proprioception may be less important during turning. Thus, sensory reliance patterns during quiet stance may not accurately reflect patterns seen during turns.



Disclosures: C. Duppen: None. **K. Shaab:** None. **A. Flach:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.01/BB15

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: SECIHTI CF-2023-G-243
SECIHTI CIORGANISMOS-2025-92

Title: Mild maternal separation induces stress-dependent metaplasticity of adrenal chromaffin-cell coupling

Authors: *P. SEGURA-CHAMA[1], V. S. HERNANDEZ[2], L. MEJÍA[2], L. ZHANG[2];
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Abstract: Early-life experiences can shape the future responsiveness of neuroendocrine systems to stress. We investigated whether mild neonatal maternal separation (MS) induces long-term alterations in adrenal chromaffin-cell plasticity that become evident only after subsequent adult stress exposure. Rat pups underwent maternal separation (3 h/day, PND2-15) using a mild paradigm in which dams were removed before pups were transferred to a temperature-controlled incubator. In adulthood (PND150), animals were exposed to an 8-day unexpected mild stress (UMS) protocol consisting of alternating forced swim stress, Morris water maze, sleep deprivation, and restraint stress.Basal adrenal expression of connexin-36 (Cx36) and connexin-43 (Cx43) did not differ between animal-facility-reared (AFR) and MS rats. However, following UMS, MS animals displayed significantly increased chromaffin-cell Cx36 and Cx43 immunoreactivity compared with AFR controls. The effect was particularly pronounced in females. In parallel, MS animals exhibited enhanced corticosterone responses to restraint stress, suggesting altered adrenal recruitment during adult stress adaptation.Because our previous studies demonstrated persistent potentiation of the hypothalamic vasopressin system after maternal separation, including increased AVP expression and structural remodeling of the paraventricular and supraoptic nuclei, we examined potential adrenal substrates associated with stress-dependent remodeling. PACAP-immunoreactive fibers were abundant within the adrenal medulla and showed extensive spatial association with Cx43-positive chromaffin-cell territories. Unexpectedly, dense PACAP innervation and numerous Cx43-positive plaques were also observed in the zona reticularis, suggesting previously unrecognized corticomedullary microdomains.These findings support the concept that mild early-life stress establishes a latent developmental adaptation that modifies the future responsiveness of adrenal chromaffin-cell networks. The data further identify PACAP-rich adrenal territories as candidate substrates for stress-dependent remodeling of chromaffin-cell communication and endocrine responsiveness.

Disclosures: P. Segura-Chama: None. **V.S. Hernandez:** None. **L. Mejía:** None. **L. Zhang:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.02/BB16

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R15MH125282

Title: Estradiol withdrawal after a hormone simulated pregnancy increases dopamine release and uptake in the nucleus accumbens core

Authors: H. FISHER[1], C. MURRELL[1], R. A. ESPAÑA[2], ***L. E. BEEN**[1];
[1]Haverford Col., Haverford, PA; [2]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Estrogen levels increase dramatically across pregnancy, but rapidly drop to pre-pregnancy levels after birth. The resulting postpartum "estrogen withdrawal" state has been shown to contribute to the etiology of postpartum mood and anxiety disorders. Previous research in our lab and others has shown that postpartum estradiol withdrawal affects the nucleus accumbens (NAc) and motivated behaviors. However, specific neural mechanisms connecting peripartum estradiol fluctuations to brain and behavioral changes are not well understood. We used a hormone-simulated pseudopregnancy (HSP) in adult female C57BL/6 mice to model postpartum estradiol withdrawal and characterized mesolimbic dopamine dynamics in the NAc with ex vivo fast-scan cyclic voltammetry (FSCV). Adult female mice were ovariectomized and given daily hormone injections that approximate estradiol levels during pregnancy. In one group of animals, estradiol was withdrawn following HSP, simulating the rapid drop in estradiol during the postpartum period. In another group, estradiol levels were sustained at high levels after HSP. Both groups were compared to a control group that received vehicle injections throughout the duration of the experiment. Five days after the animals were split into withdrawn or sustained conditions, animals were euthanized and dopamine release and uptake parameters were measured with FSCV and analyzed using Peak & Decay modeling. Following single-pulse stimulation, estradiol withdrawal increased maximal dopamine release (peak height) and increased uptake speed (tau, T20, decay slope) in the NAc core compared to animals that received sustained high levels of estradiol during the simulated postpartum period. These results were specific to the NAc core, as dopamine dynamics did not vary with hormone condition in the NAc shell. Likewise, following multi-pulse stimulation (25 and 100 Hz), estradiol withdrawal increased dopamine release (peak height) and increased uptake speed (T20, decay slope) in the NAc core compared to sustained animals. These results are supported by our previous findings showing that estradiol withdrawal following HSP increases DeltaFosB, a marker of stable plasticity following repeated dopamine stimulation, specifically in the NAc core. Taken together, these data suggest that estrogen withdrawal-dependent changes in tonic and phasic dopamine signaling are an important part of the mechanism mediating long-term plasticity in the mesolimbic dopamine pathway during the early postpartum period.

Disclosures: H. Fisher: None. **C. Murrell:** None. **R.A. España:** None. **L.E. Been:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.03/BB17

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Effects of semaglutide on body weight in patients with diabetes and obesity in a hospital in Mexico

Authors: *I. E. JUAREZ-ROJOP[1], G. V. JUÁREZ[2], J. CRUZ-CASTILLO[3], E. RODRIGUEZ-SANCHEZ[6], G. NOLASCO-ROSALES[4], Y. HERNANDEZ-DIAZ[5];
[1]Univ. Juárez Autonoma De Tabasco, Villahermosa, Tabasco, Mexico; [2]Clinica Benigno, Clinica Benigno, Mexico; [3]Univ. Juárez Autónoma de Tabasco, DACS, Mexico; [4]División Académica de Ciencias de la Salud, Univ. Juárez Autónoma de Tabasco, Villahermosa, Mexico; [5]Univ. Juárez Autónoma de Tabasco, DAMJM, Mexico; [6]HOSPITAL DE ALTA ESP. GUSTAVO A. ROVIROSA, VILLAHERMOS, TAB, Mexico

Abstract: Effects of semaglutide on body weight in patients with diabetes and obesity in a hospital in Mexico. G. LANDERO-SANCHEZ, I.E. JUAREZ-ROJOP., G.E. VILLAR-JUAREZ, RODRIGUEZ-SANCHEZ, YAZMIN HERNANDEZ-DIAZ, G.A.; NOLASCO-ROSALES, J.D.; CRUZ-CASTILLO, M.A. JIMENEZ-SANTO, Diabetes is a worldwide public health problem, and new pharmacological approaches are being developed for diabetes treatment. In this context, semaglutide is a glucagon-like peptide receptor agonist (GLP-1 RA) that stimulates insulin secretion, delays gastric emptying, and decreases appetite through neuroendocrine pathways. The clinical effects of semaglutide are glycemic control and body weight reduction. Although Mexico has a high prevalence of diabetes and obesity, the evidence about GLP-1 RA effects in the Mexican population is limited. The objective of this study was to evaluate the effect of semaglutide on body weight reduction in patients with type 2 diabetes and obesity. We conducted a longitudinal study and recruited 15 patients from the diabetes clinic of the Hospital Regional de Alta Especialidad “Dr. Gustavo A. Rovirosa Pérez”. The evaluated individuals began treatment with an oral semaglutide dose of 7 mg/day. Anthropometric measurements, body composition, and biochemical parameters were evaluated at baseline and after three months of drug use. Treatment effects were analyzed using a paired Student's t-test ($p < 0.05$). The recruited population was predominantly female (12 women), with a mean age of 50.8 ± 13.62 years and a mean age at diabetes diagnosis of 36.73 ± 8.82 years. A significant decrease in body weight (91.54 ± 20.80 kg vs. 89.15 ± 20.90 kg) was observed in these patients after three months of semaglutide treatment. Likewise, waist and hip circumferences decreased by 2.20 cm and 3.27 cm, respectively; this effect was more pronounced in women. Importantly, a trend toward muscle mass loss (1.49 kg) was observed in all subjects. Regarding glycemic control, patients showed a significant 1.3% decrease in HbA1c ($p = 0.03$). These findings suggest

that semaglutide is a good pharmacological alternative for body weight and glycemic control in patients with type 2 diabetes and obesity in the Mexican population.

Disclosures: I.E. Juarez-Rojop: None. **G.V. Juárez:** None. **J. Cruz-Castillo:** None. **E. Rodriguez-Sanchez:** None. **G. Nolasco-Rosales:** None. **Y. Hernandez-Diaz:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.04/BB18

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: ZIA NS002824-35

Title: Tanycyte ablation disrupts fertility and GnRH terminal integrity in the mouse median eminence

Authors: *D. CABRAL DA SILVA[1], S. WRAY[2];
[1]NINDS - NIH, Bethesda, MD; [2]Cell. & Developmental Neurobio., NIH NINDS, Bethesda, MD

Abstract: Tanycytes are specialized radial glial cells lining the third ventricle walls of mediobasal hypothalamus. Due to their strategic location, they coordinate signal exchange between the circulatory system and the brain. Previous studies have demonstrated that tanycytes are essential for the maintenance of the estrous cycle through estrogen receptor expression and by regulating the access of GnRH terminals to the portal vasculature in a cycle-dependent manner. However, how tanycytes integrate reproductive and metabolic cues remains unclear. Here, we investigated their necessity for reproduction and assessed how tanycyte loss impacts GnRH terminals in the median eminence. Tanycyte-specific ablation was induced in Rax-CreER/Eno2-lsl-DTA/Ai9 (Tny-DTA) mice and Rax-CreER/Ai9 served as wild-type controls (WT). Recombination was activated using a tamoxifen-chow (250 mg/kg; Envigo Teklad #TD.130856) administered from postnatal day 42 for 3 weeks, followed by 3 weeks of standard chow before experiments. Immunocytochemistry confirmed the absence of tdTomato expression in tanycytes of the median eminence in Tny-DTA mice. DAPI staining revealed reduced cell density along the third ventricle wall. In breeding trials, all WT pairs produced two litters within 8 weeks. In contrast, one Tny-DTA pair showed a 2-week delay and only one litter, while the other one failed to conceive. Pup weight differed between groups, although litter size was preserved. The vaginal smears analysis showed a disrupted pattern of estrous cycle on Tny-DTA mice, where they stayed on diestrus for longer periods than the WT. These findings indicate that ablation of median eminence tanycytes disrupts reproductive function in mice, highlighting their critical role in reproductive regulation.

Disclosures: D. Cabral da Silva: None. **S. Wray:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.05/BB19

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: 82471738
82071603
82271732
82201888

Title: Kisspeptin-GnRH response mediates reproductive adaptations to physiological hormonal transitions and nutrition stress

Authors: Y. ZENG[1], Y. HUANG[2], ***L. WANG**[3];
[1]Shanghai Ninth People's Hosp. affiliated to Shanghai Jiaotong Univ., Shanghai, China; [2]The Ninth People's Hosp. affiliated to Shanghai Jiaotong Univ., Shanghai, China; [3]The Ninth People's Hosp. affiliated to Shanghai Jiaotong Univ., Shang Hai, China

Abstract: In vivo reproductive adaptations to physiological hormonal transitions and nutritional stress remain unclear; this study is the first to investigate these adaptations through the lens of the kisspeptin-GnRH (gonadotropin-releasing hormone) response. We used pharmacology, in vivo electrophysiology, chemogenetics, and serial LH measurements in freely moving mice to assess reproductive neuronal activity and LH secretion during physiological estrous transitions, short-term fasting, diet-induced obesity (DIO), and semaglutide treatment.We demonstrate that GnRH neuronal responsiveness is hormonally gated, peaking during the proestrus and diestrus phases. Nutritional challenges induced distinct adaptive responses: although short-term fasting lowered baseline and peak firing rates, it preserved kisspeptin sensitivity. In contrast, DIO severely reduced baseline firing and induced profound kisspeptin resistance. Crucially, DIO mice remained fully responsive to direct chemogenetic activation, localizing the functional defect to upstream kisspeptin signaling rather than intrinsic neuronal dysfunction. Furthermore, both acute fasting and semaglutide treatment successfully restored kisspeptin responsiveness and downstream LH secretion in obese mice.These findings delineate reproductive adaptations to physiological hormonal transitions and nutritional stress. By pinpointing upstream kisspeptin signaling as the primary site of metabolic impairment, this study identifies a key neural mechanism linking metabolic state to reproductive function and suggests potential therapeutic targets for obesity-associated infertility.

Disclosures: Y. Zeng: None. **Y. Huang:** None. **L. Wang:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.06/BB20

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: 82271732
82201888
82471738
82071603

Title: Progesterone prevents premature LH surge/ovulation by readjusting GnRH neuron activity

Authors: X. SHEN[1], ***Y. HUANG**[3], L. WANG[2];
[1]The Ninth People's Hosp. affiliated to Shanghai Jiaotong Univ., Shanghai, China; [2]The Ninth People's Hosp. affiliated to Shanghai Jiaotong Univ., Shang Hai, China; [3]Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China

Abstract: Progesterone is widely used in progestin-primed ovarian stimulation (PPOS) protocols to prevent premature luteinizing hormone (LH) surges, yet the central neural mechanisms underlying this effect remain incompletely understood. We investigated how progesterone regulates hypothalamic neuronal activity and LH secretion using a mouse model of PPOS.c-fos TetTag mice were used to map neuronal activation patterns during the periovulatory period. Activated hypothalamic neurons were isolated by fluorescence-activated cell sorting and subjected to transcriptomic analysis. Immunofluorescence, qPCR, serial LH measurements, pharmacological manipulation, and in vivo electrophysiological recordings of GnRH neurons were performed to evaluate neuroendocrine responses.PPOS completely suppressed the preovulatory LH surge without affecting basal LH levels. Neuronal activity mapping revealed reduced activation in the preoptic area and enhanced activation in the arcuate nucleus (ARC). Transcriptomic analysis identified significant upregulation of Sirt1 and suppression of reproductive neuroendocrine pathways in activated ARC neurons. In vivo electrophysiology demonstrated that progesterone increased basal GnRH neuronal firing but prevented the transition to the high-frequency firing pattern associated with LH surge generation. Pharmacological inhibition of SIRT1 reduced hypothalamic Sirt1 expression but failed to fully restore LH surge generation, suggesting that ARC SIRT1 contributes to, but does not solely mediate, progesterone-induced reproductive suppression.These findings demonstrate that progesterone suppresses the preovulatory LH surge through central neuroendocrine mechanisms involving ARC activation, SIRT1 signaling, and reprogramming of GnRH neuronal activity. The results provide mechanistic insight into the hypothalamic actions of progesterone during ovarian stimulation.

Disclosures: X. Shen: None. **Y. Huang:** None. **L. Wang:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.07/BB21

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH Grant R01NR019417

Title: How Hormones Affect Immune Cell Populations in a Diverse Sample of Healthy Adults

Authors: *S. Q. STOCKING[1], C. K. WEBB[1], S. R. GUNAPATI[1], H. L. PAYNE[1], A. M. PIPER[1], N. M. GOLDFEIZ[1], A. ROYCHOWDHURY[1], S. K. TOTSCH[1], T. L. QUINN[1], N. C. BORGOGNA[1], M. B. THOMEER[2], L. A. NORIAN[3], B. R. GOODIN[4], R. E. SORGE[1]; [1]Psychology, [2]Sociology, Univ. of Alabama at Birmingham, Birmingham, AL; [3]Microbiology, Immunology, and Mol. Genet., Univ. of Kentucky, Lexington, KY; [4]Anesthesiol., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: There are sex-based differences in the susceptibility to chronic pain and autoimmune diseases, with those assigned female at birth often showing the highest burden. In mice, the maintenance of chronic pain is dependent on sex hormone levels and specific leukocyte populations, with males utilizing microglia and females utilizing T cells. Notably, T cells are key contributors to many autoimmune conditions, which are typically more prevalent in females. This biological, sex-based difference in immune cell usage is often equated to a socially constructed, sex-based difference but may be more appropriately characterized as a result of predominant circulating hormones. However, past studies have either enrolled only cisgender adults and/or excluded those on exogenous hormones. Given the increased prevalence of hormone use across multiple populations and the impact of sex hormones on immune cells populations, it is important to assess these associations in healthy adults with known levels of circulating endogenous and/or exogenous hormones. The present study aimed to investigate the role of sex hormones on immune cell populations in healthy adults. Eligible participants (N= 119) included cisgender men (n= 29) and women (n= 34), transgender men (n= 14) and women (n= 15), and non-binary individuals (assigned female at birth, n= 13; assigned male at birth, n= 11) between the ages of 18-65 who reported no chronic pain or autoimmune conditions. After a blood draw, plasma was used to assess leukocyte populations (flow cytometry) and sex hormone levels (multiplex assays). Preliminary data analyses showed that testosterone levels were associated with the frequency of NK cells and CD3+, CD4+, activated CD4+, activated CD8+ cells, and regulatory T cells, such that those with lower testosterone levels had higher frequencies of all T cell types and lower frequencies of NK cells. Sex assigned at birth (SAB; male/female) was associated with testosterone levels and regulatory T cell frequency, but it was not associated with other immune cell population levels. However, gender (man/woman) was associated with testosterone levels as well as frequency of CD3+ and CD4+ T cells, as well as NK cells. These preliminary findings suggest that the previously observed sex differences in chronic pain and autoimmune conditions may be due to circulating hormone levels and are more reflective of gender (whether cisgender or transgender) than SAB. Together, these data suggest that the introduction of exogenous hormones (e.g., hormone replacement therapies, testosterone use in aging men, etc.) may impact immunological systems and affect risk for chronic pain and autoimmune conditions.

Disclosures: S.Q. Stocking: None. **C.K. Webb:** None. **S.R. Gunapati:** None. **H.L. Payne:** None. **A.M. Piper:** None. **N.M. Goldfeiz:** None. **A. Roychowdhury:** None. **S.K. Totsch:** None. **T.L. Quinn:** None. **N.C. Borgogna:** None. **M.B. Thomeer:** None. **L.A. Norian:** None. **B.R. Goodin:** None. **R.E. Sorge:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.08/BB22

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: UNAM-PAPIIT-IT200125

Title: Chronic liraglutide administration alters hypothalamic neural activation, hydrosaline homeostasis and stress-related behaviours in adult rats

Authors: *I. HERNÁNDEZ-ARAIZA[1], V. S. HERNANDEZ[2];
[2]Dept. of Physiology, Fac. of Med., [1]Natl. Autonomous Univ. of Mexico, Mexico City, Mexico

Abstract: Glucagon-like peptide-1 receptor (GLP-1R) agonists, like liraglutide, are widely used to treat metabolic disorders. Recent studies suggest they also reduce vasopressin synthesis and release, potentially affecting hydrosaline homeostasis. Previous work shows that vasopressinergic magnocellular neurons (AVP-MNNs) project to extrahypophyseal regions, including the hippocampus, lateral habenula, amygdala and locus coeruleus, areas involved in learning, memory, anxiety and motivation. Here, we investigated metabolic, renal, and behavioral consequences of chronic liraglutide treatment in male and female Wistar rats. A furosemide-treated group was included to determine if the observed effects were due to its diuretic action. Rats received daily saline, furosemide (10 mg/kg) or liraglutide (200 µg/kg) injections for 4 weeks ($n \geq 8$/group). Body weight was recorded weekly, daily food and water intake were monitored. Renal and systemic homeostasis were assessed by kidney weight, urine and plasma osmolarity. Liraglutide significantly reduced body weight in both sexes. Furosemide induced weight loss only in females. Liraglutide reduced daily food intake without affecting water intake or relative kidney weight, no effects of furosemide were observed. Urine osmolarity decreased 3h after liraglutide injection at both the beginning and end of treatment. Furosemide reduced urine osmolarity and urine Na^+ only at treatment onset. To evaluate chronic effects, rats were subjected to a 24h wash-out period before a water deprivation protocol. Liraglutide- and furosemide-treated rats showed reduced basal urine osmolarity (0h WD), but reached control levels after 24h WD. However, only liraglutide-treated rats showed increased plasma osmolarity. Spatial learning in the Morris water maze was unaffected. The liraglutide-treated males displayed increased anxiety-like behavior in the elevated plus maze and reduced learned helplessness in the forced swimming test (FST). Furosemide-treated rats did not differ from controls. Following FST, liraglutide-treated males showed altered Fos expression patterns in the paraventricular and supraoptic nuclei and in AVP-MNN target regions. These results indicate

that chronic liraglutide treatment induces metabolic effects, persistently alters fluid homeostasis, and selectively modulates stress-like behaviors in a sex-dependent manner, highlighting interactions between GLP-1 signaling, hydroelectrolytic homeostatic circuits and stress regulation.

Disclosures: I. Hernández-Araiza: None. **V.S. Hernandez:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.09/BB23

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Field-Spicer Fellowship in Research

Title: Bisphenol-F exposure at environmentally relevant levels during the perinatal through juvenile period impacts neuromuscular physiology and behavior of rats

Authors: A. GANDHI, A. TAYLOR, X. GUIMBA, A. ALMOND, S. KALASAVA, L. RICHARDSON, E. SENKOWSKI, S. WACHOWICZ, J. SMITH, D. DYKHUIS, L. HANSON, G. NEAL, J. ESCHTRUTH, ***G. M. LANGE**;
Saginaw Valley State Univ., University Center, MI

Abstract: In classic work by William C. Young's research laboratory, it was established that organization of mammalian brain morphology is guided by gonadally expressed hormones both in-utero and continuing into the perinatal environment. This suggests, while the genetic sex of an organism may drive development of sexual morphology and the brain, the environment also can and shape phenotypic expression. Bisphenol-F is a chemical agent found in many plastics used in everyday life. Use of bisphenol-F has increased in recent years in comparison to the primary bisphenol used in industry, bisphenol-A, due to concerns about known environmental and physiological effects of bisphenol-A exposure. Bisphenol-F can and does leach from plastics and is inadvertently ingested by organisms. Bisphenol-F has been identified as an endocrine disruptor and has the potential to alter the neuroendocrine system of developing organisms. We theorize that perinatal through juvenile exposure to bisphenol-F may influence phenotype by reshaping organization of the mammalian central nervous system altering expression of morphology and reproductive behavior. In this research, exposure to bisphenol- F occurred at environmentally relevant levels during post parturition days 21-60. At maturity, neuromuscular development was assessed and neurobehavioral responses related to anxiety were examined. Additionally, the presence and timings of reproductive behaviors were measured. We have identified ways in which bisphenol-F alters development in ways that are different from that of bisphenol-A exposure. Significant findings include decreased neuromuscular strength in males exposed to bisphenol-F and metabolism related weight gain in females exposed to bisphenol-F.

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Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.10/BB24

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: SECIHTI-Mexico (CBF2023-2024-732)
DGAPA-UNAM (PAPIIT IN220825)

Title: Thyrotropin-releasing hormone-degrading ectoenzyme is necessary for optimal response of the hypothalamus-pituitary thyroid axis to fasting and anorexic effects of TRH and Taltirelin during refeeding in rodents

Authors: V. PÉREZ, A. CASTRO-TRON, A. COTE-VELEZ, R. M. URIBE, P. I. JOSEPH-BRAVO, *J.-L. CHARLI;
Inst. de Biotecnologia, UNAM, Cuernavaca, Mexico

Abstract: Thyrotropin-releasing hormone (TRH) is inactivated by the narrow specificity TRH-degrading ectoenzyme (TRH-DE), a peptidase mainly expressed by neurons in the brain where it can control the amount of TRH in the extracellular space. It is also expressed by β2-tanycytes of the hypothalamic median eminence, near TRH nerve terminals but its expression does not appear critical for the control of the hypothalamus-pituitary-thyroid (HPT) axis in basal conditions. However, it constrains the magnitude of the cold-induced serum TSH concentration, a stimulus that activates the HPT axis (Endocrinology, 150, 2283, 2009; Cells, 14(10), 725, 2025). During fasting, TRH-DE activity increases in rat β2-tanycytes, possibly contributing to diminished serum TSH concentration (Endocrinology, 156, 2713, 2015). To unravel TRH-DE physiological role during and post fasting, we tested the impact of reducing or eliminating TRH-DE in adult rodents on a) the response of the HPT axis to fasting, and b) the anorectic effect of ip TRH (Metabolites, 14(6), 302, 2024) and Taltirelin (TAL), a peptidase resistant analogue, on refeeding post fasting. In male rats fasted for 46 h, injection of the specific TRH-DE inhibitor phosphinic-TRH reversed the reduction of serum concentration of TSH. Fasting reduced pituitary *Tshb* expression in both WT and *Trhde* KO male mice but *Tshb* levels were higher in KO than WT mice; it also reduced serum T3 concentration in WT but not in KO male mice. In addition, we observed differences in response to fasting in the expression of deiodinases (key enzymes for thyroid hormones synthesis) and genes related to lipid metabolism. Many of these effects were sexually dimorphic. In male and female WT mice, ip TRH reduced post-fasting food intake; the effect of TAL was more potent and prolonged than that of TRH, consistent with TRH-DE activity controlling TRH effect on food intake. Surprisingly, instead of being

amplified, TRH and TAL effects were not detected in *Trhde* KO mice. When TRH or TAL were injected near the dorsomedial nucleus of hypothalamus (DMH), we observed that they reduced refeeding post fasting in WT but not in KO male mice. The peripheral injection of TRH or TAL increased the number of cFOS+ cells in the DMH in wild type male mice, while in *Trhde* KO mice the number of cFOS+ cells was elevated at baseline and was not further increased by TRH or TAL. These results show that TRH-DE is required for maintenance of central sensitivity to TRH, a correct adjustment of the HPT axis to fasting with sexually dimorphic impacts, and possibly for development of the circuit that controls the anorexic effect of TRH.

Disclosures: V. Pérez: None. **A. Castro-Tron:** None. **A. Cote-Velez:** None. **R.M. Uribe:** None. **P.I. Joseph-Bravo:** None. **J. Charli:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.11/BB25

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: USDA Animal Health and Disease Research Formula Funding, NIFA

Title: Neuroendocrine modulation of the female HPG-axis during neonatal mini-puberty: suppression of hypothalamic kisspeptin neurons in the porcine model using subcutaneous sex-steroid implants

Authors: *C. SOLOMON[1], L. CRISPELL[1], C. KOJIMA[2], B. WHITLOCK[1];
[1]Large Animal Clin. Sci., [2]Animal Sci., The Univ. of Tennessee, Knoxville, TN

Abstract: Current sterilization procedures in livestock and companion animals rely on surgical removal of the gonads, using techniques such as ovariectomy and orchiectomy in females and males, respectively. These procedures are invasive, painful, and resource-intensive, requiring anesthesia, an appropriate environment, and trained personnel. Growing concerns over animal welfare, companion animal overpopulation, and management of feral and invasive species have created demand for alternative sterilization methods that are less resource-dependent and technical. Recent studies in female mice, dogs, and male pigs demonstrated that administration of sex steroids during the neonatal period, 'mini puberty', can inhibit reproductive development long-term. The proposed mechanism involves kisspeptin (Kp) neurons in the arcuate nucleus (ARC) of the hypothalamus. These neurons reside at the top of the hypothalamic-pituitary-gonadal (HPG) axis, which is the neuroendocrine pathway for sexual maturation and reproduction. In the ARC, Kp neurons operate in a feedback loop with circulating sex steroids to generate pulses of gonadotropin-releasing hormone (GnRH). This study examined the effects of exogenous sex steroids administered neonatally on hypothalamic Kp neurons in female pigs. We hypothesized that steroid exposure during the 'mini puberty' period would reduce ARC Kp neurons. Eighteen neonatal pigs [postnatal day (PND 3)] were treated subcutaneously with either

a sham implant [Control (CON, n = 9)] or estradiol [(16 mg) + trenbolone acetate (80 mg), Implant (IMP), n = 9]. Hypothalami were collected at PND 24 and cryosectioned for Kp immunohistochemistry; fewer ARC Kp neurons were observed in IMP subjects [3.54 ± 0.97 (SE)] than in CON subjects [63.43 ± 3.72] ($p<0.0001$). Serum samples were collected at PND 3 and 24 to determine hormone concentrations [luteinizing hormone (LH), anti-Müllerian hormone (AMH), and estradiol]. Serum estradiol concentrations were greater in the IMP group ($p<0.0001$). No difference was observed in serum concentrations of LH ($p=0.9015$) or AMH ($p=0.3580$) between CON and IMP. After pigs were euthanized on PND 24, the uterus and ovaries were weighed, and the reproductive tracts of the IMP group [7.95 g ± 0.55] were larger than those of the CON [3.10 g ± 0.1] ($p<0.001$). The results of this study confirm that exogenous steroid administration during the neonatal period suppresses ARC Kp neurons, indicating that sex steroid administration during this period may be a promising non-invasive alternative. This study was limited to the first month following birth; future studies should assess long-term effects on reproductive development.

Disclosures: C. Solomon: None. **L. Crispell:** None. **C. Kojima:** None. **B. Whitlock:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.12/BB26

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: SECIHTI (INFRASTRUCTURE 2022, ID 322333 TO FC)
SECIHTI CVU 1004334

Title: Insights into the selectivity of rapid estrogen actions modulating the micturition reflex in female rabbits

Authors: *F. CASTELÁN[1], S. SANCHEZ MENESES[2], A. FLORES HERNANDEZ[4], D. L. CORONA QUINTANILLA[3], E. CUEVAS[5], M. MARTINEZ-GOMEZ[6];
[1]Inst. de Investigaciones Biomédicas, UNAM, Tlaxcala, Mexico; [2]Univ. Autónoma de Tlaxcala, Chiautempan, Mexico; [3]Univ. Autónoma de Tlaxcala, Tlaxcala, Mexico; [4]Univ. Autonoma de Tlaxcala, Tlaxcala, Mexico; [5]Ctr. Tlaxcala De Biología De La Conducta, Ctr. Tlaxcala De Biología De La Conducta/Universidad Autónoma De Tlaxcala, Tlaxcala, Mexico; [6]Inst. de Investigaciones Biomédicas UNAM, Tlaxcala, Mexico

Abstract: We have previously approached the ability of rapid estrogen actions to modulate pelvic floor muscles in female rabbits. The present study aimed to determine the estrogen receptor involved. To do this, anesthetized female rabbits were used to simultaneously record bladder pressure and reflex activity of the pelvic floor muscles. The results revealed that the local application of selective estrogen agonists modulates the reflex activity of specific pelvic floor muscles. In addition, some of the urodynamic variables were affected. These findings suggest

that selective rapid estrogen actions directly influence the viscerosomatic reflexes that underlie micturition.

Disclosures: F. Castelán: None. **S. Sanchez Meneses:** None. **A. Flores Hernandez:** None. **D.L. Corona Quintanilla:** None. **E. Cuevas:** None. **M. Martinez-Gomez:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.13/BB27

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NSF IOS-1933264
Wilczynski-Georgia Research Alliance Fellowship
MSU start-up funds

Title: Cesarean birth alters efferent projections associated with the hypothalamic paraventricular nucleus

Authors: A. MONA, H. PRINGLE, ***A. CASTILLO-RUIZ**;
Michigan State Univ., East Lansing, MI

Abstract: Birth is an extraordinary event for placental mammals and occurs during a period when critical developmental processes, including neuronal cell death, are actively shaping the brain. We previously reported that, compared with newborn vaginally delivered mice, Cesarean-born mice exhibit increased neuronal cell death in the paraventricular nucleus of the hypothalamus (PVN). This effect is associated with fewer vasopressin (VP) neurons in the PVN during adulthood, suggesting that Cesarean birth can influence neurodevelopment in ways that produce lasting changes in the VP system's circuitry. To test this hypothesis, we generated male and female mice born vaginally or via Cesarean section and collected their brains in adulthood. We then processed the tissue for the histochemical detection of VP and quantified VP fiber density in brain regions that receive projections from the PVN: the bed nucleus of the stria terminalis (BNST), medial preoptic area (mPOA), lateral septum (LS), and medial amygdala (MeA). As expected, we found that Cesarean birth altered VP innervation, but in a brain region and sex dependent manner. Specifically, within the posterior portion of the BNST, which plays a role in regulating social recognition and stress behaviors, we found that Cesarean-born males have decreased VP fiber density. Similarly, in the mPOA, a brain region involved in parental and sex behavior, Cesarean-born mice had decreased VP density regardless of sex. Next, since VP from the PVN is also released in the periphery as a hormone, we used high-performance liquid chromatography to assess VP in the blood of the same mice. However, there was no effect of Cesarean birth on this measure. Thus, our results suggest that Cesarean birth alters the central release of VP originating from the PVN and that, therefore, this system may be functionally compromised. In support, in work presented last year at this conference, we show that Cesarean

birth alters huddling, nest building, and locomotion. These are all behaviors associated with the VP system of the PVN via efferent projections to areas including the posterior BNST and mPOA. Our studies are of clinical relevance given the widespread practice of Cesarean delivery across the world.

Disclosures: A. Mona: None. **H. Pringle:** None. **A. Castillo-Ruiz:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.14/BB28

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: UNAM-DGAPA-PAPIIT IN 204225
SECIHTI CBF-2025-I-830

Title: The cholinergic neurons of the nucleus basalis magnocellularis regulate ovarian functions

Authors: R. CALDERÓN RAMOS[1,2,5], M. RODRÍGUEZ[6], S. PÉREZ[7], I. TORRES[8], *C. C. SILVA-MENDEZ[3,5], E. VIEYRA VALDEZ[9], L. MORALES-LEDESMA[4];
[2]Posgrado en Ciencias Biológicas, [1]Univ. Nacional Autónoma De México, Mexico City, Mexico; [3]Univ. Nacional Autónoma De México, Ecatepec DE Morelos, Mexico; [4]Biol. of Reproduction Res. Unit, Univ. Nacional Autónoma De México, Mexico, Mexico; [5]Med. Surgeon Career, Facultad de Estudios Superiores Zaragoza, Mexico City, Mexico; [6]Biol. of Reproduction Res. Unit, Facultad de Estudios Superiores Zaragoza, Ciudad de México, Mexico; [7]Biol. of Reproduction Res. Unit, Facultad de Estudios Superiores Zaragoza, Nezahualcóyotl, Mexico; [8]Biol. of Reproduction Res. Unit, Facultad de Estudios Superiores Zaragoza, CDMX, Mexico; [9]Nursing Career, Facultad de Estudios Superiores Zaragoza, Ciudad de México, Mexico

Abstract: In mammals, ovarian functions depend on a series of neuroendocrine signals originating in the hypothalamus, where gonadotropin-releasing hormone (GnRH) neurons are located. These neurons are modulated by several neurotransmitter systems, including the cholinergic system. It has been reported that cholinergic signaling is involved in the regulation of GnRH-neuron activity and, consequently, reproductive functions; however, the origin of these cholinergic inputs remains unclear. One potential source is the nucleus basalis magnocellularis (NBM), a structure primarily associated with cognitive processes such as learning and memory, since it sends cholinergic projections to brain regions involved in the regulation of GnRH neurons. Therefore, the aim of this study was to determine whether the NBM participates in the control of ovarian function. To this end, 90-day-old female CII-ZV rats received bilateral microinjections of saline (Vehicle) or quinolinic acid (NBMx; 200 μM; excitotoxic agent that destroys cholinergic cells) into the NBM on the morning of proestrus (09:00 h). An intact group was also included. The effects of the lesion were evaluated during the estrus phase 7 to 12 days after surgery. Lesion of the NBM reduced the percentage of animals displaying regular estrous

cycles (Intact: 8/8, Vehicle: 7/8, NBMx: 2/8) and completely blocked ovulation (Intact: 8/8, Vehicle: 8/8, NBMx: 0/8). In addition, the lesion reduced the number of ovarian follicles (Intact: 144, IQR: 125–155; Vehicle: 159, IQR: 137–175, NBMx: 96, IQR: 88–110) and decreased progesterone (Intact: 36.19 ± 6.44; Vehicle: 39.50 ± 3.88, NBMx: 18.50 ± 3.87) and estradiol serum levels (Intact: 26.57 ± 4.76; Vehicle: 25.25 ± 3.10, NBMx: 7.83 ± 1.18). These findings suggest that the NBM is a critical component of the neural and neuroendocrine circuits regulating ovarian steroid secretion, follicular development, and ovulation.
This work was supported by UNAM-DGAPA-PAPIIT IN 204225 and SECIHTI under grant number CBF-2025-I-830

Disclosures: R. Calderón Ramos: None. **M. Rodríguez:** None. **S. Pérez:** None. **I. Torres:** None. **C.C. Silva-Mendez:** None. **E. Vieyra Valdez:** None. **L. Morales-Ledesma:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.15/BB29

Topic: I.09. Spatial Navigation

Support: JUST Grant No. 794/2024

Title: Metabolic Dysfunction and Cognitive Decline in a Rat Model of Type 2 Diabetes

Authors: *K. NUSEIR, B. ALSAMARAH, R. KHADER;
Jordan Univ. of Sci. and Technol., Irbid, Jordan

Abstract: Background Diabetes Mellitus (DM) comprises a group of metabolic disorders. Type 2 DM (T2DM), strongly associated with obesity and dietary habits, represents a major global health challenge. Cognitive impairment is a recognized complication of poorly controlled DM; however, its underlying mechanisms remain incompletely understood. This study aimed to investigate T2DM-induced cognitive dysfunction using a rat model that closely mimics human T2DM. **Methods** Forty-eight male and female Sprague-Dawley rats were allocated into two groups: high-fat diet (HFD) group combined with low-dose streptozotocin (STZ) and a regular diet (RD) control group. The two groups further stratified into four groups according to sex. HFD rats received a diet rich in fat and fructose water for 21 weeks, followed by an intraperitoneal STZ injection (40 mg/kg). Body weight and metabolic parameters, including fasting blood glucose (FBG), fasting insulin (FI), and insulin resistance (HOMA2-IR), were assessed. Behavioral tests were performed after 15 weeks to evaluate cognitive and related functions. At the end of the experiment, hippocampal and serum levels of oxidative stress and neurodegeneration markers (Brain derived neurotrophic factor (BDNF), Neurotrophin-3 (NT-3), β-amyloid, Matrix metaloprotenase 9 (MMP9), Phosphorylated tau (P-tau) and Advanced glycation end products (AGEs) were analyzed. **Results** Results demonstrated that HFD significantly increased body weight ($p < 0.0001$), FBG ($p < 0.0001$), and insulin resistance ($p <$

0.0001), accompanied by cognitive impairment as evidenced by behavioral testing (spatial learning and memory, p=0.0011). Biomarker analysis further supported the presence of hippocampal oxidative stress and neurodegenerative changes (BDNF, MMP9, P.tau, β-amyloid, p<0.05). **Conclusion** These findings highlight the detrimental impact of diet-induced metabolic dysfunction on cognitive health and provide insights into potential mechanisms linking T2DM and cognitive decline.

Disclosures: K. Nuseir: None. **B. Alsamarah:** None. **R. Khader:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.16/BB30

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: T32 NIEHS Training Grant - T32ES07046
North Carolina State University Start-Up Funds Awarded to Dr. Natalia Duque-Wilckens
CHHE Pilot Grant - P30ES025128

Title: The Impact of Perinatal Microplastic Exposure on Mast Cells, Neurodevelopment, and Body Weight in Neonatal and Adolescent Mice

Authors: *H. DIXON-ZARZOUR[1], J. X. FRANGES[2], L. RACKOWITZ[2], M. COWLEY[2], J. E. MEITZEN[2], N. DUQUE-WILCKENS[2];
[1]Biol. Sci., [2]Dept. of Biol. Sci., North Carolina State Univ., Raleigh, NC

Abstract: Microplastics (MP) are pervasive and persistent environmental contaminants that can cross physiological barriers and membranes to accumulate in the brain, immune organs, and mucosal tissues. Recent literature has detected MPs in placental and reproductive tissues, highlighting the neurotoxic, pro-inflammatory, and metabolic impacts of developmental exposure. However, these studies use non-translational dosing paradigms via oral gavage and often fail to isolate the perinatal period as a distinct window of vulnerability. A potential driver of these effects is the mast cell (MC), a tissue-resident innate immune sentinel able to react to environmental contaminants. Research has demonstrated the pro-inflammatory impacts of MP exposure on MCs within the innate immune system, though MC-specific MP literature remains limited. To address these gaps in knowledge, C57BL6/J pregnant dams were dosed ad libitum with control, vehicle (0.1% Tween-80), or experimental (10^6ng MP/ L) drinking water to replicate a chronically ingested low dose (0.01-0.03 mg/kg/day). Exposure was terminated at tissue collection for neonates (PN12) or weaning (PN21) for adolescent pups. We hypothesized that perinatal MP exposure will impact MCs, neurodevelopment, and body weight in neonatal and adolescent mice. Body weight recorded from birth until tissue collection detected no impacts from perinatal MP exposure in neonates or adolescents. Survival reflexes assessed in neonates

showed a significant increase in percent surface righting failure at PN6 but no change in negative geotaxis at PN9 in MP exposed pups. Mesenteric analysis demonstrated no impact of perinatal MP exposure on MC density and activation in neonates; however, baseline plasma histamine levels were significantly decreased compared to control and vehicle. Preliminary data in late adolescent pups (PN40 to PN48) similarly demonstrates blunted Passive Systemic Anaphylaxis responses following perinatal MP exposure. Together, these findings suggest a granule release or histamine-specific impact following perinatal MP exposure. Future directions will continue to discern the impacts of perinatal MP exposure on plasma histamine levels, mesenteric MC density and activation, anxiety-like behaviors, and cognitive function in late adolescent pups.

Disclosures: H. Dixon-Zarzour: None. **J.X. Franges:** None. **L. Rackowitz:** None. **M. Cowley:** None. **J.E. Meitzen:** None. **N. Duque-Wilckens:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.17/BB31

Topic:

Support: NIH Grant R01 U01ES035843
Center for Human Health and the Environment P30 ES-025128

Title: Perinatal Exposure to FireMaster 550 Impacts D1-Dopamine Receptor Influence Upon Medium Spiny Neuron Electrophysiology in the Nucleus Accumbens Core of Female And Male Prairie Voles (Microtus ochrogaster)

Authors: *E. BRADEMAN, J. MEITZEN;
Biol. Sci., North Carolina State Univ., Raleigh, NC

Abstract: Environmental contaminants such as flame retardants are increasingly implicated in neurodevelopmental disruption, with growing evidence suggesting that exposure can impact brain function. Firemaster 550 (FM 550), a flame retardant, is of concern due to its ubiquity and evidence that perinatal exposure can disrupt socioemotional behaviors later in life. These behaviors are regulated by neuromodulatory activity within the nucleus accumbens (NAcc), a key component of the social brain neural network that mediates social reward and motivation. D1- and D2-dopamine receptor (DR) signaling in the NAcc plays critical roles in regulating complex social behaviors such as pair bonding and alloparental care. These behaviors have been extensively studied in prairie voles (Microtus ochrogaster), a socially monogamous rodent species. However, FM 550's impacts on the dopaminergic system and consequent electrophysiology remain unknown. To address this gap, we used whole-cell patch-clamp electrophysiology to examine whether perinatal FM 550 exposure alters DR modulation of NAcc medium spiny neuron (MSN) intrinsic excitability in female and male voles. We hypothesize that perinatal FM550 exposure modifies neuronal responsiveness to D1-DR stimulation. Dams were

given a daily dose of vehicle or 1000 μg of FM 550 throughout gestation and lactation. NAcc MSN D1-DR function was then assessed in offspring via application of the D1-DR agonist SKF-38393 in acute brain slices, where resting membrane potential (RMP), action potential (AP) rate, and input resistance were assessed. We found SKF-38393 significantly depolarized RMP and increased AP generation in only FM 550-exposed animals. AP count in FM 550 animals was significantly higher on average following D1-DR activation compared to control animals. These findings suggest that perinatal FM 550 exposure alters D1-DR modulation of NAcc MSN excitability, making cells more sensitive to D1-DR activation. Future work will confirm the specificity of SKF-38393 and investigate D2-DR signaling. Understanding how environmental contaminants alter dopaminergic function may help explain mechanisms underlying impacts upon relevant socioemotional behaviors.

Disclosures: E. Brademan: None. **J. Meitzen:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.18/BB32

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: T32GM133366
CHHE P30 ES-025128
NC State Startup Funds

Title: EFFECTS OF PERINATAL FM550 EXPOSURE ON SOCIAL BEHAVIORS AND NEURAL MAST CELL-ASSOCIATED GENE EXPRESSION IN PREPUBERTAL MALE AND FEMALE MICE

Authors: *Y. TANG, J. MEITZEN;
Biol. Sci., North Carolina State Univ., Raleigh, NC

Abstract: Neurodevelopmental disorders involving impacts on social behaviors are increasing in incidence, calling for rigorous assessments of the root causes. Recent human and animal studies have implicated environmental contaminant exposure as a potential cause. One relevant contaminant is Firemaster 550 (FM550), a household flame retardant. Perinatal FM550 exposure has been shown to alter social and anxiety-like behaviors in adult rodent offspring, with disruption of neurodevelopmental processes as an underlying cause. Here, we investigate whether this disruption extends to mast cells, an immune cell type located throughout the brain and body. Mast cell disruption has been linked to deficits in adult rodent social and anxiety-like behaviors. Given this previous emphasis on adult animals, here we focus upon prepubertal animals, an overlooked yet critical developmental phase in social behavior. We hypothesize that perinatal exposure to FM550 impacts prepubertal offspring social preference behavior in the context of mast cell activation, concomitant with impacts on mast cell-associated gene

expression. To test this hypothesis, we exposed dam C57BL/6J mice to 0 or 625 ug FM550 daily via an oral treat from gestation to offspring weaning at PND 21. Prior to behavioral testing, offspring received an IgE-DNP antibody injection to initiate a mast cell-mediated immune response. Male and female offspring underwent social preference testing at PND 28, after which dorsal hippocampal and hypothalamic tissues were collected. Mast cell-associated gene (cKit, cma1, hdc, hrh1, and hrh3) expression was measured via qPCR. No significant sex differences were found in the behavior or gene expression data. We found IgE-DNP stimulation increased mouse social preference in control mice. However, social preference and vigilance values were attenuated in the FM550 dosed group compared to the control. Gene expression analysis of the dorsal hippocampus revealed that IgE-DNP stimulation increases ckit, hdc, and hrh1 expression independent of perinatal FM550 exposure. Overall, we show that perinatal exposure to FM550 impacts offspring social preference in the context of IgE-DNP challenge. These results implicate mast cells as an important target for future investigations into the mechanisms underlying the impacts of environmental contaminants on brain and body function and behavior.

Disclosures: Y. Tang: None. **J. Meitzen:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.19/CC1

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: P30 ES-025128
R01 MH-109471
NC State University Provost Professional Experience Award

Title: A machine learning based exploration of estrous cycle modulation of electrophysiological properties in nucleus accumbens medium spiny neurons

Authors: A. RAINA, ***J. MEITZEN**;
North Carolina State Univ., Raleigh, NC

Abstract: Machine learning models (MLMs) have been extensively employed to classify neuron types using electrophysiological attributes. What has been much less explored is using these methods to assess differences within a neuron type, especially in the context of subtle changes induced by natural neuromodulatory cycles such as the female rodent estrous cycle. Previous research indicates that the estrous cycle induces shifts in adult female rat nucleus accumbens (NAc) medium spiny neuron (MSN) electrophysiological properties, including spike bursts, passive membrane properties, and miniature excitatory post-synaptic current (mEPSC) attributes. We took data from across the four estrous phases from each recording type (n=4,073 bursts, n=5,348 passive, n=61,060 mEPSC) and extracted biologically relevant features. Within each data type, we employed seven MLMs (Random Forest, Gradient Boosting, Logistic Regression,

k-Nearest Neighbors, Multi-Layer Perceptron, Support Vector Classifier, Decision Tree Classifier) to classify features across estrous phase. After training, the per-class recall and classification accuracy of each model were assessed to further understand the discriminative capacity of models with respect to individual phases. Furthermore, we conducted feature importance analysis of the most successful model (Random Forest) and latent space visualization of each feature set. We found that: (a) Select MLMs can classify MSN estrous phase origin with up to 94% accuracy (Random Forest on passive features); (b) The diestrus and late proestrus phases had the most distinct electrophysiological properties; (c) MLM accuracy differed substantially by model type and feature set, with passive features yielding highest performance (94%), followed by spiking (83%), and mEPSC (69%); (d) Feature importance analysis revealed input resistance, burst length, and baseline current were most discriminative for their respective datasets. These findings demonstrate that MLMs can detect neuronal changes associated with the estrous cycle and are useful tools for assessing nuanced electrophysiological differences within a neuron type and across a hormonal cycle. They further represent an additional application of MLMs as a tool to understand the state variables underlying biological processes, as model accuracy becomes a computational metric for how profoundly different cellular properties are modulated by hormonal state.

Disclosures: A. Raina: None. **J. Meitzen:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.20/CC2

Topic:

Support: National Institutes of Health (NIH) Grants U01 ES035843
Center for Human Health and the Environment P30 ES-025128
NC State University Chemistry of Life Training Program T32GM141887

Title: Perinatal FireMaster 550 (FM 550) Exposure Increases Inwardly Rectifying Potassium Channel Currents in Medium Spiny Neurons in the Nucleus Accumbens Core of Male and Female Prairie Voles (Microtus ochrogaster).

Authors: *E. GAETA, J. MEITZEN;
Biol. Sci., North Carolina State Univ., Raleigh, NC

Abstract: Perinatal exposure to environmental contaminants has been shown to impact neuronal development and its subsequent function, leading to changes in behavior. One example contaminant is FireMaster 550 (FM 550), a chemical flame retardant commonly found in household products such as carpets, foam-based furniture, and baby products. In a prosocial laboratory model animal, the prairie vole (Microtus ochrogaster), perinatal exposure to FM 550 resulted in sex-specific behavioral impacts on offspring's prosocial behaviors, including pair

bonding. Prior research showed that perinatally exposed voles as adults exhibited differential electrophysiology in medium spiny neurons (MSNs) within the nucleus accumbens (NAcc), an important brain region for regulating social behaviors, compared to vehicle animals. MSNs showed differences in responsiveness to inhibitory stimuli, specifically an FM 550-induced decrease in the rectified range input resistance of both sexes. However, the ionic mechanism underlying this difference is unknown. We hypothesized that the differences observed between FM 550-exposed and vehicle animals resulted from a functional change in inwardly rectifying potassium (IRK) channels. To test this hypothesis, dams were exposed to vehicle or 1000 μg of FM 550 throughout gestation and lactation via treat ingestion. Whole-cell patch clamp electrophysiology was employed to assess MSN IRK channel function via application of cesium chloride (CsCl), a known IRK channel blocker, in NAcc acute brain slices. Results showed a significant increase in cesium-sensitive IRK current density at the most hyperpolarized potential (-120 mV) in FM 550-exposed animals. With a significant increase in the percent change of input resistance, before and after CsCl application, at -120 mV in FM 550-exposed animals. Additionally, there was a significant difference in normalized conductance and input resistance after CsCl application in all cells. This study supports the hypothesis that perinatal FM 550 exposure impacts IRK channel function. Future studies will attempt to investigate the potential genetic differences causing the functional change as evidenced in this study. Here, we demonstrate a novel impact of a pervasive environmental contaminant on ion channel function long after exposure has ceased.

Disclosures: E. Gaeta: None. **J. Meitzen:** None.

Poster

PSTR102: Neuroendocrine Anatomy and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR102.21/CC3

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/NIMH Grant R01MH142540
NIH/NIDA Grant R01DA058653
NSF/CAREER Grant 2235858

Title: Context and state-dependent human decision-making: validatory computational analyses across individuals, cohorts, and potential neuroeconomic translation with rodent models.

Authors: *C. HEATON[1], L. RAKOCEVIC[2], R. IBÁÑEZ ALCALÁ[1], K. GOOSENS[3], A. FRIEDMAN[4];
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Abstract: Abnormal and maladaptive decision-making tendencies are transdiagnostic markers of numerous neuropsychiatric disorders, yet mapping these processes is heavily confounded by individual variability in valuation and interpretation of stimuli and mismatched cross-species paradigms. We validated the empirical utility of the Human Model for Analyzing Neuroeconomic Situations (HUMANS), a web-based testing framework, focused on individual computational profiling and explored a potential methodology for cross-species translation through neuroeconomic principles. Evaluating 250 participants, the platform successfully resolved distinct individual decision-shifts that primarily fit either sigmoidal or bell-shaped valuation trajectories. At the group level, raw approach rates shifted as expected across tasks. Crucially, non-choice behavioral and biometric data, like reaction times and normalized saccadic frequency, were significantly modulated by macro narrative task context but remained invariant across changes in reward and cost levels, indicating that behavioral kinetics respond to cognitive framing rather than each tradeoff conflict. The baseline framework demonstrated absolute sex neutrality across all choice, kinetic, and autonomic metrics when examining a sex-balanced cohort. Finally, abstracting and normalizing human choice data onto an equidistant 4x4 utility grid revealed striking structural symmetry with an automated rodent paradigm that similarly offered 4 distinct levels of cost and rewards that were paired. Together, these findings demonstrate that the HUMANS framework provides a sensitive, robust tool to quantify choice behavior across contexts, offering a foundation for future neuroimaging, clinical telemedicine screening, and adaptive digital therapeutics.

Disclosures: C. Heaton: None. **L. Rakocevic:** None. **R. Ibáñez Alcalá:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.01/CC4

Topic: G.08. Food and Water Intake and Energy Balance

Support: Border Biomedical Research Center
UTEP College of Science (MLQ)
Research Incentive Funds (AMK)
MERITUS Program - Campus Office for Undergraduate Research/Office of the Provost (ARAM)

Title: Three-Dimensional Light Sheet Microscopy Analysis of GLP-1 Neuronal Populations in the Rat Hindbrain and Comparison with Atlas-Registered Two-Dimensional Sections and NeuN staining

Authors: *A. ARVIZU MORALES[1], G. P. TAPIA[4], M. L. QUINTANA[2], S. BALIVADA[3], A. M. KHAN[2];
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Paso, TX; [3]Univ. of Texas at El Paso, El Paso, TX, ; [4]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX

Abstract: The rat brain has served as a foundational model for investigating neural circuits controlling feeding and metabolic homeostasis. Glucagon-like peptide-1 (GLP-1) expressing neurons of the caudal brainstem are known to regulate feeding behavior and energy balance, yet their volumetric distribution within hindbrain structures remains incompletely characterized. Most existing studies rely on two-dimensional histological sections, which limit appreciation of the full 3-D architecture of these neuronal populations.To address this, we employed light sheet fluorescence microscopy to visualize GLP-1 neuronal populations in intact hindbrain tissue. Brain tissue from adult male Sprague-Dawley rats was immunolabeled for GLP-1 using an Alexa Fluor 647-conjugated secondary antibody. Cleared tissue was imaged to generate volumetric datasets capturing GLP-1-immunoreactive neurons throughout the caudal brainstem, preserving spatial relationships across multiple anatomical axes with minimal photodamage. These 3-D data were compared with previously generated two-dimensional atlas-registered datasets, in which hindbrain tissue was sectioned at 30 μm and processed for immunohistochemistry, mapping GLP-1-positive perikarya within coronal sections corresponding to levels defined in the Brain Maps 4.0 rat brain atlas. To facilitate cross-modality comparison, the 3-D volume was computationally sectioned in coronal, sagittal, and horizontal planes mirroring traditional histological orientations, enabling direct visual and spatial comparison between datasets and with NeuN staining performed in a separate light-sheet-imaged brain. Preliminary analysis confirms preservation of the known GLP-1 distribution within the nucleus of the solitary tract while revealing spatial continuity into adjacent regions including the medullary reticular formation. By bridging volumetric light sheet imaging with atlas-based two-dimensional histology, this work contributes toward a more complete structural framework for understanding GLP-1 neuronal organization and may facilitate future functional studies on the neural control of feeding and energy homeostasis.

Disclosures: A. Arvizu Morales: None. **G.P. Tapia:** None. **M.L. Quintana:** None. **S. Balivada:** None. **A.M. Khan:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

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Program #/Poster #: PSTR103.02/CC5

Topic: G.08. Food and Water Intake and Energy Balance

Support: Border Biomedical Research Center
UTEP College of Science (MLQ)
Department of Computer Science
Research Incentive Funds (AMK)

Title: The Good, The Bad, and the Slice: An open-access pipeline for extracting and segmenting 2-D images from 3-D Imaris light sheet microscopic image data

Authors: *I. ACEDO AGUILAR[1], M. QUINTANA[2], S. BALIVADA[2], A. M. KHAN[2], O. FUENTES[2];
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Abstract: Neuroscientists rely on visualization tools like Imaris® from Oxford Instruments to be able to visualize data obtained from light-sheet microscopy. These 3-D data generated from a stitched set of images of a rat brain are very large, usually being over 100 GB. This 3-D object is then sliced in a specific plane using Imaris® tools to be exported as a TIFF image. This process is very time consuming for researchers. Open-access software like ImageJ or Fiji can then be run to count cells or perform other analyses. Here we present an open-access pipeline to generate a large dataset of images from an Imaris® file using a pair of two different Python scripts inside a Jupyter notebook environment. In Extract.ipynb and an Imaris® 3-D-object file, one can route the object to the workflow and obtain as many images as desired, select the thickness of the image, and the resolution, to extract cross-sections in three planes; coronal, sagittal, and horizontal. This script will be able to extract large amounts of data at a fraction of the time required in Imaris. With the images extracted, one can use Segmentation.ipynb; this script combines three different publicly available segmentation models; Mediapipe, Segment Anything model 2 (SAM2), and Cellpose. While Mediapipe in this use case was not useful in our testing, presumably because it was not originally designed for microscopy data, SAM2 effectively identified macro-structures inside the images. In contrast, Cellpose proved the most effective identifying cells inside the images, which greatly enabled cell counting. In conclusion, the tests show that our pipeline was not only successful in extracting image data at a high resolution from an Imaris® file, but was also able to run segmentation models that will aid researchers with limited access to Imaris®.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

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Topic: G.08. Food and Water Intake and Energy Balance

Support: Border Biomedical Research Center
UTEP SMART MIND Program – NIH Grant R25DA033613 (BA)
Research Incentive Funds (AMK)

Title: Hypocretin/orexin and catecholaminergic systems in the adult male rat midbrain and hindbrain: a standardized atlas-based mapping of reciprocal circuitry

Authors: *B. ARSLAN[1], J. PALACIOS[1], S. BALIVADA[2], A. M. KHAN[1];
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Abstract: Catecholaminergic (CA) neurons are critical mediators of the counterregulatory response to hypoglycemia, feeding control, arousal, and stress. These neurons span noradrenergic (A1-A7), adrenergic (C1-C3), and dopaminergic (A8-A10) cell groups, identifiable by dopamine beta hydroxylase (DBH) for noradrenergic, phenylethanolamine N-methyltransferase (PNMT) for adrenergic, and tyrosine hydroxylase (TH) for dopaminergic neurons, respectively. Our previous work established standardized delineations of hindbrain CA populations, including DBH-immunoreactive noradrenergic and PNMT-immunoreactive adrenergic cell groups, registered to the Swanson Brain Maps 4.0 (BM4.0) atlas (LW Swanson, J Comp Neurol., 2018). Hypocretin/orexin (H/O)-expressing neurons of the lateral hypothalamic area innervate CA cell groups throughout the brainstem onto adrenergic C1-C3 and noradrenergic A1, A2, and A6 neurons, as well as TH-immunoreactive dopaminergic neurons of the VTA. Yet the reciprocal relationship between H/O and CA systems has not been characterized within a standardized framework across midbrain and hindbrain. Here we extend our atlas-based approach to examine this relationship. Triple-label fluorescence immunohistochemistry using TH, PNMT, and H/O antibodies was performed on adult male rat tissue sections. We imported photomicrographs of our immunostained sections into Adobe Illustrator, where we carefully aligned them with digital BM4.0 atlas templates. The histochemical data from a cohort of male rats were manually annotated and registered to BM4.0 using a high-spatial resolution approach to preserve the intricate distribution patterns we observed. This approach distinguishes dopaminergic (TH+/PNMT−) from adrenergic (TH+/PNMT+) neurons while mapping H/O fiber contacts onto CA cell groups and CA fibers onto H/O neurons. Based on prior heatmap data, we propose H/O innervation will concentrate at C1-C3 in the hindbrain and overlap with TH-immunoreactive neurons in the VTA. This bidirectional atlas-registered analysis will provide the first standardized map of H/O-CA reciprocal circuitry in the rat brainstem, advancing understanding of the neuroanatomical organization underlying arousal, feeding, and the counterregulatory response to hypoglycemia with implications for therapeutic targets in preclinical metabolic disease models.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

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Topic: G.08. Food and Water Intake and Energy Balance

Support: Border Biomedical Research Center
UTEP SMART MIND Program – NIH Grant R25DA033613 (JP/BA)
Research Incentive Funds (AMK)
BUILDing SCHOLARS Program (JP)

Title: Atlas-based neurochemical investigation of opioid and catecholaminergic circuit elements in rat ventral tegmental area and surrounding regions

Authors: *J. PALACIOS[1], B. ARSLAN[1], S. BALIVADA[2], A. M. KHAN[1];
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Abstract: Opioid use disorder is an urgent neurological and public health crisis. Repeated exposure floods the brain's reward circuitry with dopamine, triggering neuroadaptations that drive tolerance and anhedonia, a downward spiral that can end in overdose. Addressing this crisis requires safer, non-opioid alternatives, yet progress remains limited by an incomplete understanding of how opioid and dopaminergic circuits are organized within the brain's reward-mediating regions. The ventral tegmental area (VTA) is a key midbrain node of the mesolimbic dopamine system and a critical site where opioid signaling may influence reward and addiction; however, the precise spatial relationships between opioid and catecholaminergic pathways within this region remain poorly characterized. To address this issue, we examined the neurochemical architecture of the rat VTA using fixed and frozen 30-micron-thick tissue sections from adult male Sprague-Dawley rats. We conducted double-label immunohistochemical experiments utilizing antibodies raised against the mu-opioid receptor (MOR), met-enkephalin (MET), and tyrosine hydroxylase (TH), markers selected to delineate the spatial relationship between opioid signaling and dopaminergic cell populations. Photomicrographs of immunostained sections were aligned to an adjacent Nissl-stained tissue series serving as a cytoarchitectural reference for registration to a rat brain atlas (Brain Maps 4.0; L. W. Swanson, J Comp Neurol, 2018). Immunolabeled elements were manually traced at high spatial resolution using Adobe Illustrator to generate detailed neuroanatomical maps. Our results show that TH, MOR, and MET immunoreactivities (-ir) display distinct and at times opposing spatial distributions within the rat midbrain. Notably, MOR is largely absent from TH-positive fibers extending beyond the VTA, and a dense MOR-ir fiber bundle identified in the hypothalamic-tegmental tract at level 36 in Brain Maps 4.0 highlights a discrete anatomical site where opioid signaling appears spatially segregated from presumptive dopaminergic pathways. These findings contribute to our understanding of how opioid and dopaminergic circuits are organized within the VTA, helping to more precisely pinpoint anatomical targets for the development of opioid-alternative therapies with reduced addiction liability.

Disclosures: J. Palacios: None. **B. Arslan:** None. **S. Balivada:** None. **A.M. Khan:** None.

Poster

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Topic: G.08. Food and Water Intake and Energy Balance
UTEP College of Science (SB)
UTEP SMART MIND Program – NIH Grant R25DA033613 (CS)
Research Incentive Funds (AMK)

Title: Spatial organization and atlas-based mapping of parvalbumin-immunoreactive neurons in the rat olfactory bulb and prefrontal cortex

Authors: *C. SEGOVIANO[1], S. BALIVADA[2], A. M. KHAN[3];
[1]Biol. Sci., The Univ. of Texas at El Paso, El Paso, TX; [2]Univ. of Texas at El Paso, El Paso, TX, ; [3]Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Parvalbumin-containing interneurons are a specialized class of inhibitory interneurons in the brain that express parvalbumin (PV), a calcium binding protein. PV interneurons are the primary mediators of feedforward and feedback inhibition, using rapid inhibition to control timing, synchrony, and information flow. In the olfactory bulb, these interneurons shape odor discrimination and temporal coding, while in the prefrontal cortex they are essential for working memory and cognitive control. We have previously conducted preliminary work studying PV immunoreactivity in certain portions of the prefrontal cortex (K Negishi et al., SfN Abstracts 2016). Here we elaborate further on this work by systematically mapping and characterizing PV interneuron organization across both the olfactory bulb and prefrontal cortex. To begin this effort, we performed optimization experiments for antibodies against PV in adult male Sprague-Dawley rats. Employing immunohistochemical markers with 2-D visualization methods allowed us to examine PV cell populations across multiple levels for both olfactory bulb and the prefrontal cortex. Utilizing a spatially-proximate Nissl-stained tissue series allowed precise alignment to digital brain atlas templates alongside our immunohistochemical data. This allowed us to accurately register the location of PV interneuron populations to a standardized spatial framework (L.W. Swanson, Brain Maps 4.0, J Comp Neurol., 2018; BM4.0). In addition to PV, antibody optimization experiments were conducted for additional neurochemical markers to examine their spatial organization relative to PV populations across these regions. Additionally, data recorded across subjects was spatially averaged to generate consensus maps, establishing a standardized neuroanatomical framework for PV-containing interneuron distribution across the olfactory bulb and prefrontal cortex. These data will provide an atlas-registered baseline for PV interneuron distribution across olfactory and prefrontal subdivisions currently absent from rat neuroanatomical literature, serving as a foundation for future investigations into olfactory-prefrontal inhibitory circuitry.

Disclosures: C. Segoviano: None. **S. Balivada:** None. **A.M. Khan:** None.

Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH NIDDK 7F32DK134121-04

Title: Agranular Insular Cortex Projections to the Dorsal Raphe Encode Interoceptive States and Regulate Energy Balance

Authors: *A. MELGAR, K. MCDERMOTT, Y. XU;
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Abstract: The anterior insular cortex (AIC) integrates interoceptive and environmental information, while the dorsal raphe nucleus (DRN) is a major serotonergic hub implicated in feeding behaviors and energy balance. Although the AIC sends direct projections to the DRN, the functional role of this pathway remains poorly defined. Here, we investigated anatomical connectivity, activity patterns, and functional relevance of the AIC →DRN circuit. Retrograde tracing confirmed projections from the AIC to the DRN. To assess circuit activity patterns, fiber photometry recordings of GCaMP fluorescence were obtained during behavioral assays including water and food consumption, acute stress, and in different environments including warm, cold, and anxiogenic. Function assessments were made using chronic inhibition (Kir2.1) and acute chemogenetic activation (DREADDs) models. Results revealed robust responses during state-dependent activity with stronger responses in the left hemisphere. Activity increased during water consumption, thermal challenges, and feeding-related behaviors, including food bout initiation in the fed state and food approach and consumption in the fasted state, and was rapidly suppressed following food bout termination. Acute stress elicited similar responses across hemispheres. In contrast, responses during anxiety-like exploration were modest, with increased activity upon center entry in the open field test and limited or delayed responses in the elevated plus maze. Chronic inhibition of AIC→DRN neurons reduced body weight gain in both sexes, with increased brown adipose tissue temperature observed in females. Acute activation increased food intake in both fed and fasted states. These findings identify the AIC→DRN pathway as a cortical circuit that selectively encodes interoceptive drive and regulates feeding and energy expenditure, providing a framework for targeting upstream cortical control of serotonergic systems to more precisely modulate energy balance.

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Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant R00DK133560

Title: Melanocortin-3 receptor neurons in the central nucleus of the amygdala linking feeding and affective behaviors

Authors: *K. D. CALDARONE[1,2], K. M. CASIANO[1,2], A. CABALLERO[1,2], M. N. BEDENBAUGH[1,2];

[1]Dept. of Neurosci., [2]Evelyn F. and William L. McKnight Brain Inst., Univ. of Florida, Gainesville, FL

Abstract: Feeding, anxiety, and stress-related disorders are prevalent, frequently comorbid conditions that profoundly impact physical and mental health. While significant evidence suggests that the systems controlling feeding and affective behaviors are linked, the organization of the underlying neural circuitry remains unclear. One brain region positioned to modulate these behaviors is the central nucleus of the amygdala (CEA). Our prior work demonstrated that cell bodies expressing the melanocortin-3 receptor (MC3R) are abundantly expressed in the CEA. Further, MC3R has been revealed to bidirectionally regulate feeding and anxiety and its deletion results in metabolic disturbances, including adverse responses to fasting, disrupted feeding behaviors, and an enhanced behavioral anorexia phenotype in stress-induced anorexia paradigms. Significantly, CEA^{MC3R} neural circuitry is uncharacterized both anatomically and functionally. Using a mouse model, we began characterizing CEA^{MC3R} neural circuitry by mapping projection patterns of these neurons using anterograde viral tracing combined with whole brain tissue clearing, immunolabeling, and lightsheet microscopy. CEA^{MC3R} neurons send dense projections to regions involved in homeostatic regulation, emotional processing, and autonomic functions, including the lateral hypothalamus, bed nucleus of the stria terminalis, lateral habenula, and pontine reticular nucleus. To test potential functional roles, Fos induction experiments, confocal imaging, and analyses of percent MC3R/Fos colocalization in the CEA were conducted. Consistent with roles in feeding and affective behaviors, Fos was induced in CEA^{MC3R} neurons during refeeding after a 24 hour fast, restraint stress, and acute inescapable foot shock stress (n = 8 mice per condition, 4 mice per sex). Analyses using Imaris suggest differential recruitment of CEA^{MC3R} neurons, with medial CEA populations more active during feeding and capsular CEA populations active during stress. Altogether, these data have led us to hypothesize that CEA^{MC3R} neurons may serve as an integrative node linking metabolic and emotional state signals to coordinate adaptive behavioral responses to environmental challenges. Ongoing SmartAnalytics analyses are evaluating sex-dependent differences in CEA^{MC3R} projections that may contribute to distinctions in feeding and affective behaviors. Future work employing chemogenetic manipulation using excitatory and inhibitory DREADDs will establish the causal contribution of CEA^{MC3R} neurons to behavior during feeding and emotionally salient behavioral paradigms.

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Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant R00DK133560

Title: Age-dependent changes in brain-wide neural activation and microglial expression in response to acute fasting

Authors: *B. M. ANDERSON, J. I. RODRÍGUEZ, K. D. CALDARONE, M. N. BEDENBAUGH;
Dept. of Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Approximately 22.7% of older adults experience Anorexia of Aging (AA) which is caused by changes in appetite, metabolic regulation, and immune signaling in the brain. AA can increase the risk of other health issues, including malnutrition, frailty, and sarcopenia. Aging is also accompanied by an increase in neuroinflammation. This is caused by the overactivation of microglia, the brain's resident immune cells, which can negatively impact neuronal function. In our research, we aim to better understand the causes behind the deterioration of the hunger response in old age, with the intention of finding methods to prevent it. We hypothesize that chronic neuroinflammation around metabolic circuits may be involved in the deterioration of the hunger response. To test this, we used an unbiased whole-brain approach to compare neuronal activity (Fos) and microglial expression and morphology (Iba1) in young and aged mice under fasted and *ad libitum* feeding conditions. Preliminary analyses showed the preoptic area (POA) of the hypothalamus and the arcuate nucleus (ARH) of the hypothalamus as having notable differences between young and aged mice under fasted conditions. There were distinct differences in brain-wide microglial morphology between young and aged mice, regardless of feeding condition. Aged mice also exhibited increased Fos labeling in amygdalar regions in response to the fasting condition. To build upon our whole brain analysis findings, we conducted preliminary immunohistochemistry experiments to quantify if the expression of a peptide known to play a role in the hunger response, agouti-related peptide (AgRP), changed in the POA and ARH as animals age. Quantifying AgRP terminals in the POA and ARH revealed a slight trend towards increased levels of AgRP in aged mice as compared to young mice. Preliminary results also validate our whole brain findings and show a much lower level of neural activation in the POA of aged mice versus young mice under fasted conditions, as well as a higher density of microglial cells in the ARH of aged mice, regardless of feeding condition. Altogether, these preliminary findings suggest that age-related neuroinflammation, particularly within hypothalamic metabolic circuits, may disrupt normal hunger signaling, supporting the hypothesis that microglial dysregulation may contribute to the deterioration of the hunger response in Anorexia of Aging.

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Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant DP2AI177891

Title: Single-Cell Mapping of the Mosquito Central Brain Identifies Neurons Driving Blood Feeding

Authors: *Y. JIAO[1], T. R. SORRELLS[2];
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Abstract: Mosquitoes are among the deadliest animals in the world, threatening millions of people by transmitting pathogens that cause Malaria, Zika, and Dengue through their bites. Preventing mosquito bites remains one of the most effective strategies for halting the spread of these mosquito-borne diseases. However, the neural mechanisms driving blood feeding behavior are still poorly understood, in part because traditional model animals do not exhibit this behavior. Mosquitoes rely on multiple sensory cues such as CO2, human odors, and heat to locate and approach humans. The neuron circuits in their brain processing the integration of these sensory inputs are therefore the key to understanding mosquito blood-feeding behavior.To investigate this, we generated single-cell transcriptomic profiles of the central brain of mosquitoes exposed to CO_2, heat, or both stimuli simultaneously, using immediate early gene expression as a proxy to identify activated neurons. CO_2 is a long-range cue that induces persistent host-searching behavior. We found that 1.9% of central brain neurons were activated following CO_2 exposure, with a significant enrichment of dopaminergic neurons, suggesting that dopamine plays an important role in mediating long-range host-searching. Heat, by contrast, is a short-range cue. When presented alone, heat elicited a minimal neural response, with only 0.5% of neurons activated, indicating that heat-responsive neurons are gated by activity from neurons responding to other stimuli. Simultaneous exposure to both CO_2 and heat was sufficient to induce substantial blood engorgement, and we observed activation of 5.1% of central brain neurons under these combined conditions. Among the neurons activated exclusively or synergistically by the combined CO_2 and heat stimulus, we identified mushroom body neurons and peptidergic neurons, highlighting their potential roles in multisensory integration and driving blood-feeding behavior.

Disclosures: Y. Jiao: None. **T.R. Sorrells:** None.

Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant DK142148

Title: Circuit Organization of Tachykinin-1-Expressing Neurons in the Parasubthalamic Nucleus

Authors: *S. KATZEV[1], P. COFFIN[1], M. CARTER[2];
[2]Biol., [1]Williams Col., Williamstown, MA

Abstract: The parasubthalamic nucleus (PSTN) has emerged as an important hypothalamic node involved in the regulation of feeding, aversion, arousal, and motivated behavior. Neurons expressing tachykinin-1 (Tac1) represent the predominant neuronal population within the PSTN and play a critical role in suppressing food intake and promoting behavioral responses to aversive stimuli. Despite growing interest in $PSTN^{Tac1}$ neurons, the broader circuit architecture through which these neurons integrate information and influence behavior remains poorly understood. Here, we combined complementary viral tracing approaches to characterize both the afferent inputs to and efferent projections from $PSTN^{Tac1}$ neurons in male and female mice. To identify afferent inputs, we employed monosynaptic rabies virus tracing and identified 70 distinct upstream brain regions distributed across forebrain, midbrain, and hindbrain structures. The strongest inputs originated from regions implicated in feeding regulation, stress responses, arousal, and aversive processing, suggesting that $PSTN^{Tac1}$ neurons are positioned to integrate diverse physiological and environmental signals relevant to behavioral state. To examine efferent projections, we used Cre-dependent retrograde adeno-associated viral tracing across pairwise combinations of six major previously characterized projection targets. Most $PSTN^{Tac1}$ neurons projected selectively to individual downstream regions, indicating a high degree of output specificity. However, select projection pairs exhibited elevated collateralization, suggesting that subsets of neurons may coordinate signaling across multiple functionally related targets. Furthermore, projection-defined neuronal populations displayed partial topographic organization within the PSTN, such that anatomical position provided a probabilistic predictor of downstream connectivity. Together, these findings reveal the anatomical logic of $PSTN^{Tac1}$ circuit organization. $PSTN^{Tac1}$ neurons receive convergent input from a broad network of regions associated with internal state and environmental salience, while distributing information through largely segregated output channels with limited but strategic collateralization. This circuit architecture provides a structural framework for understanding how $PSTN^{Tac1}$ neurons integrate diverse signals and orchestrate context-dependent regulation of feeding, aversion, arousal, and motivated behavior.

Disclosures: S. Katzev: None. **P. Coffin:** None. **M. Carter:** None.

Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant DK142148

Title: Tachykinin-1 Neurons in the Parasubthalamic Nucleus Dynamically Encode and Mediate Appetite Suppression

Authors: *E. PYE[1], C. NOXON[1], M. CARTER[2];
[2]Biol., [1]Williams Col., Williamstown, MA

Abstract: The ability to suppress food intake in response to internal physiological states and external environmental demands is essential for survival. The parasubthalamic nucleus (PSTN) has emerged as an important regulator of feeding behavior, and neurons expressing tachykinin-1 (Tac1) represent the predominant neuronal population within this region. Previous studies have shown that PSTN^{Tac1} neurons are activated by feeding and aversive stimuli and are sufficient to suppress food intake, but the natural activity patterns of these neurons and their necessity across distinct forms of appetite suppression remain incompletely understood. Here, we combined fiber photometry and chemogenetic approaches to examine both the behavioral encoding and functional significance of PSTN^{Tac1} neurons in freely behaving male and female mice. To characterize neural activity during naturalistic behavior, we recorded calcium-dependent activity from PSTN^{Tac1} neurons using fiber photometry. Food consumption elicited robust and sustained increases in activity that scaled with feeding-bout duration, whereas inaccessible food cues produced weaker and more transient responses. In contrast, water consumption decreased PSTN^{Tac1} activity, while social interaction and movement initiation elicited comparatively modest activation. These findings indicate that PSTN^{Tac1} neurons dynamically encode feeding behavior in a context-dependent manner rather than simply signaling meal initiation or generalized ingestion. To determine whether PSTN^{Tac1} neurons are required for appetite suppression, we chemogenetically inhibited these neurons during multiple anorexigenic states. Inhibition increased food intake following lithium chloride-induced visceral malaise, semaglutide-induced GLP-1 receptor signaling, and cisplatin-induced chemotherapy-associated illness, but had no effect on feeding after lipopolysaccharide-induced inflammation or refeeding following food deprivation. Meal-pattern analyses suggested that these effects were driven in part by increased meal frequency, indicating a role for PSTN^{Tac1} neurons in suppressing meal initiation during specific aversive or pharmacologically induced states. Together, these findings demonstrate that PSTN^{Tac1} neurons dynamically track feeding behavior while serving as a neural substrate linking feeding behavior to anorexigenic and malaise-related signals, providing insight into illness-induced anorexia and therapeutic weight-loss mechanisms.

Disclosures: E. Pye: None. **C. Noxon:** None. **M. Carter:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.12/CC15

Topic: G.08. Food and Water Intake and Energy Balance

Support: R01 AG074092
U01 AG073148
U19 AG060917

R01 DK113627
R01 DK107670

Title: Thyroid-Stimulating Hormone Receptor and Insulin-like Growth Factor 1 Receptor Signaling as a Shared Neuromodulator Linking Feeding Behavior and Auditory Function

Authors: S. SIMS[1], M. MANSOORI[1], Z. TUMOGLU[1], A. GUMEROVA[1], G. PEVNEV[1], L. CULLEN[1], E. WEISS[1], O. MOLDAVSKI[1], F. SULTANA[1], R. PANDEY[1], G. BURGANOVA[1], S. PARTE[1], O. BARAK[1], W. ZHOU[1], T. FROLINGER[1], D. LIZNEVA[1], S.-M. KIM[1], T. SMITH[3], T. DAVIES[1], K. GOOSENS[1], T. YUEN[1], M. ZAIDI[1], R. LATIF[1], ***V. RYU**[2];
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Abstract: Thyroid-stimulating hormone receptor (TSHR) signaling has traditionally been viewed as an endocrine regulator; however, emerging evidence supports a broader role in central and peripheral physiology. Here, we demonstrate that TSHR, in coordination with insulin-like growth factor-1 receptor (IGF-1R), functions as a critical regulator of both energy homeostasis and auditory processing. Using RNAscope, we identified widespread *Tshr* expression across over 170 brain regions, with prominent enrichment in hypothalamic tanycytes—specialized glial cells that regulate blood-hypothalamus barrier (BHB) permeability and metabolic signaling. Approximately 40% of tanycytic TSHRs colocalize with IGF-1Rs, suggesting conserved receptor crosstalk. To study whether tanycytic TSHR and IGF-1R interaction affects ingestive behavior, four groups of haploinsufficient $Tshr^{+/-}$ mice were administered TSH (8 μg) intra-third ventricle (3V) with or without the IGF-1R antagonist 1H7 (8 μg). TSHR activation enhanced neuropeptide Y expression, increased ghrelin, reduced adipose depots, and promoted feeding behavior. Conversely, tanycytic TSHR knockdown by CRISPR/Cas9 inhibited feeding behavior and protected against fasting-induced body weight loss. Notably, IGF-1R blockade abolished TSH-induced hyperphagic response and pERK activation, establishing a functional requirement for TSHR-IGF-1R interaction in metabolic regulation. In parallel, we identified TSHR as a previously unrecognized regulator of auditory function independent of systemic thyroid hormone levels. *Tshr* haploinsufficient mice exhibited significant auditory deficits, including elevated auditory brainstem response (ABR) thresholds and reduced product otoacoustic emissions (DPOAE) indicative of impaired neural transmission and outer hair cell dysfunction. Consistent with these findings, *Tshr* expression was localized to key auditory structures, including cochlear cell populations and central auditory nuclei such as the ventral cochlear nucleus and superior olivary complex. These findings are clinically relevant because hearing impairment has been reported in patients treated with teprotumumab, an IGF-1R-targeting therapy. Our data suggest that disruption of TSHR-IGF-1R signaling may underlie auditory dysfunction. Collectively, our results redefine TSHR as a multifunctional signaling hub that, in concert with IGF-1R, integrates neuroendocrine control of feeding behavior and auditory function, thereby uncovering a shared signaling pathway linking metabolic control and sensory processing.

Disclosures: S. Sims: None. **M. Mansoori:** None. **Z. Tumoglu:** None. **A. Gumerova:** None. **G. Pevnev:** None. **L. Cullen:** None. **E. Weiss:** None. **O. Moldavski:** None. **F. Sultana:** None. **R. Pandey:** None. **G. Burganova:** None. **S. Parte:** None. **O. barak:** None. **W. zhou:** None. **T. Frolinger:** None. **D. Lizneva:** None. **S. Kim:** None. **T. Smith:** None. **T. Davies:** None. **K. Goosens:** None. **T. Yuen:** None. **M. Zaidi:** None. **R. Latif:** None. **V. Ryu:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.13/CC16

Topic: G.08. Food and Water Intake and Energy Balance

Support: Mellon Foundation
Trone Family Eminent Scholar Chair in Neuroscience and Behavior

Title: Impact of a High Fat/Sugar Diet on Morphine-Stimulus Control: Implications for Dysregulated Drug Intake

Authors: *K. H. JIMENEZ[1], N. GHASEM ARDABILI[1], G. WEISSBART[1], T. L. DAVIDSON[2], A. L. RILEY[1];
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Abstract: If rats are injected with a drug prior to the pairing of saccharin and the emetic lithium chloride (LiCl) and injected with saline prior to saccharin alone, they rapidly learn to avoid saccharin following the drug and to consume the same saccharin solution in its absence (for a review, see Riley et al., 2018). Such findings have been implicated in the possible within-session regulation of drug intake. That is, interoceptive drug-induced state cues present during a bout of drug taking may predict that continued or extended use leads to aversive effects and, thus, terminates a drug-taking bout (Huang et al., 2023; Huang and Riley, 2024). In this context, it might be expected that factors that impair the ability of interoceptive state cues to signal these aversive outcomes could contribute to dysregulated intake and continued /escalated consumption (Clasen et al., 2020). One such factor is consumption of an obesity-promoting high-fat/high-sugar (HF/HS) diet. For example, HF/HS diets have been reported to impair the ability of rats to discriminate interoceptive cues associated with hunger and satiety which then increase body weight, further consumption, and obesity (e.g., Lorch et al., 2024; Sample et al., 2016). The present research assessed if prior consumption of a HF/HS diet would also impair the ability of rats to utilize interoceptive signals produced by morphine administration. Male Sprague-Dawley rats raised from adolescence to adulthood on standard chow or on a HF/HS diet were trained over seven cycles in which morphine (5 mg/kg, IP) signaled a pairing of saccharin and LiCl (57 mg/kg) while saline signaled saccharin alone. In these conditions, chow-fed rats acquired the discrimination within three cycles, avoiding saccharin after morphine but consuming it after saline. Rats fed the HF/HS diet failed to learn the discrimination, consuming saccharin at high levels following both morphine and saline. While the two groups did not differ in their consumption of saccharin following saline, the group fed the chow diet drank significantly less saccharin than the HF/HS diet following morphine by Cycle 3 (although there was no differential effect of morphine on the initial cycle, suggesting no differential sensitivity to morphine). These data indicate that manipulations impacting the ability of rats to learn or utilize interoceptive cues associated with satiety or hunger also impact drug interoceptive state control of consumption.

These data support the position that disruption of interoceptive processing may be important to regulated drug intake and that factors impairing this processing may contribute, in part, to drug dysregulation, i.e., substance use disorders.

Disclosures: K.H. Jimenez: None. **N. Ghasem Ardabili:** None. **G. Weissbart:** None. **T.L. Davidson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American University. **A.L. Riley:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; American University.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.14/CC17

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Intramural Research Programs at the National Institute on Drug Abuse

Title: Ketogenic Diet Enhances Carboxylesterase-Driven Cocaine Metabolism and Attenuates Cocaine-Induced Behaviors in Rats

Authors: *R. SVARCBAHS, J. VENDRUSCOLO, L. GREER, L. LINDSAY KRYSZAK, S. JACKSON, L. F. VENDRUSCOLO, B. K. HARVEY;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Background: Carboxylesterases (CES1 and CES2) metabolize numerous xenobiotics, including cocaine, yet the impact of diet—particularly ketogenic diet (KD)—on CES activity and drug metabolism in the brain-behavior axis remains poorly understood. Recent evidence suggests that high-fat diets induce ER stress-associated exodosis of CES enzymes, raising the possibility that KD may enhance esterase-dependent cocaine metabolism. **Methods**: Using both *in vivo* and *in vitro* approaches, CES activity and cocaine pharmacokinetics were assessed in Wistar rats maintained on KD or chow. CES activity was quantified in plasma and liver using a fluorescence-based assay. Cocaine concentrations were measured in plasma, prefrontal cortex, and striatum after systemic administration. Behavioral responses were evaluated via locomotor activity following graded cocaine doses. Plasma levels of cocaine and its metabolites were measured using liquid chromatography-mass spectrometry. **Results**: KD robustly increased plasma CES activity in rats as early as 24 hours after diet initiation, with corresponding decreases in plasma and brain cocaine concentrations following cocaine injection ($p < 0.01$). KD-fed rats displayed significantly blunted cocaine-induced locomotor activity despite unchanged baseline locomotion. *In vitro* plasma assays confirmed accelerated cocaine degradation and increased production of CES-dependent metabolites, benzoylecgonine and

ecgonine methyl ester. Transcriptomic and dPCR analyses revealed KD-induced upregulation of ER stress and amino acid response pathways in liver, consistent with enhanced CES secretion. **Conclusions**: These findings identify KD as a modulator of CES-mediated cocaine metabolism, altering both pharmacokinetics and cocaine-evoked behavior. The rapid diet-dependent shifts in esterase activity highlight an underrecognized metabolic influence on drug response with implications for substance-use research and pharmacotherapy optimization.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.15/CC18

Topic: G.08. Food and Water Intake and Energy Balance

Support: R01DK134650

Title: BDNF-expressing neurons in the paraventricular and perifornical hypothalamic nuclei drive repetitive and defensive behaviors

Authors: *Y. CHEN[1], J. AN[2], B. XU[2];
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Abstract: BDNF (brain-derived neurotrophic factor) expressed in paraventricular hypothalamus (PVH) is known to regulate energy balance. Our previous studies demonstrated that activation of BDNF-expressing neurons in the PVH increased physical activity and energy expenditure, implicating this group of neurons as a potential target for obesity therapy. In this study, we investigated how PVH BDNF neurons promote physical activity. We found that the physical activity induced by activation of PVH BDNF neurons was context-dependent, only in a home cage but not in an open field. In the home cage, chemogenetic activation of PVH BDNF neurons induced self-grooming behavior and entry-blocking behavior. We are in the process of determining the identity of PVH neurons controlling these two behaviors.

Disclosures: Y. Chen: None. **J. An:** None. **B. Xu:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR103.16/CC19

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH Grant 5R01HD113522-03

Title: Rapid feed-forward activation of hypothalamic agouti-related peptide neurons by pup stimuli in lactating mice

Authors: *K. CATALBAS[1], M. A. PAYANT[2];
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[2]Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Rapid feed-forward activation of hypothalamic agouti-related peptide neurons by pup stimuli in lactating mice
Kerem Catalbas[1], Mikayla A Payant[2], Melissa J Chee[2], Patrick Sweeney[1]
1: University of Illinois Urbana Champaign, Department of Molecular and Integrative Physiology, Urbana Illinois
2: Carleton University, Department of Neuroscience, Ottawa, ON
Lactation in mammals is associated with intense energy demands on mothers, requiring a dramatic increase in food intake. In both rodents and humans, excessive energy intake during the lactational period is associated with an increased risk of metabolic dysfunction in both mothers and offspring later in life. Despite this, the precise neural circuitry and molecular mechanisms mediating increased feeding during lactation are incompletely understood. Recent findings indicate that the activity of hypothalamic agouti-related peptide (AgRP) neurons increase during lactation. This increase in AgRP neuron activity is required for promoting hyperphagia during lactation in dams, but it is not clear if sensory and/or neurophysiological mechanisms during lactation underlie increased AgRP activity. Here, we utilized a combination of RNAscope in situ hybridization, fiber photometry, and brain slice electrophysiology to characterize the sensory and neurophysiological mechanisms mediating increased AgRP neuron activity in the lactational state. We found that acute exposure to pups following a period of pup isolation rapidly increased AgRP neuron activity in lactating females. This increase in neuronal activity occurred within seconds of pup presentation and was absent in non-lactating control females. Interestingly, increased AgRP neuron activity persists when pups are visible and detectable by sensory cues but remain physically inaccessible to the dam. AgRP neuron activity further increased at the initiation of nursing, which suggested a direct effect of the suckling stimulus on AgRP neuron activity. Consistently, reintroducing pups to lactating dams after a 6-hour pup separation period increased *Fos* expression in *Agrp* neurons. Additionally, in vitro patch-clamp recordings also showed heightened excitability of AgRP neurons in dams that were reintroduced to their pups but without altering the frequency of excitatory or inhibitory synaptic inputs to AgRP neurons. Together, these findings identify pup-related sensory cues and nursing as rapid activators of hypothalamic AgRP neurons and reveal a feed-forward mechanism linking offspring-derived stimuli to maternal energy homeostasis.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR103.17/CC20

Topic: G.08. Food and Water Intake and Energy Balance

Support: The Mathers Foundation # MF-2204-02555 (Machado)
Nutrition Obesity Research Center at Harvard # NIDDK-P30-DK040561 (Machado)

Title: A Hypothalamic Pathway for Energy Conservation

Authors: A. DOUGLASS[1], N. LYNCH[2], O. RAMÍREZ PLASCENCIA[3], H. KUCUKDERELI[4], A. BANKS[5], S. HRVATIN[6], C. B. SAPER[7], ***N. L. MACHADO**[8];
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Abstract: Thermoregulation plays a vital role in the survival of animals, maintaining core body temperature (Tb) in a narrow range over the course of the day. This sophisticated and energetically costly system evolved in mammalian species, allowing thermoregulatory and metabolic adaptations to seasons of food abundance or periods of starvation. Some animals use torpor as a mechanism to suppress energy expenditure (EE) and prolong survival during periods when food supplies are limited and external temperatures are too low to sustain Tb around 37 ºC. While our recent studies identified a population of neurons in the median preoptic nucleus (MnPO) necessary for fasting-induced torpor regulation, the specific brain circuits that trigger energy conservation in response to food restriction are unknown. Here, we show that the energy state of the animal is conveyed to preoptic neurons by inputs from the arcuate nucleus (ARC), a region known to be indispensable for driving metabolic and behavioral adaptations to the fasted state. We first found that the MnPO-projecting ARC neurons expressing Agouti-Related Peptide (ARC^{AgRP}) are active during fasting-induced torpor. Moreover, activating the ARC^{AgRP}→MnPO pathway (n=5) induces a Tb decrease in both *ad libitum* (AL) or food deprived (FD) conditions (max change: -2.5 ± 0.4 °C SEM AL vs -3.1 ± 0.8 °C SEM FD), reduces energy expenditure (max change: -0.14 ± 0.04 Kcal/h SEM AL vs -0.1 ± 0.02 Kcal/h SEM FD) and suppresses brown adipose tissue thermogenesis (max change: -2.5 ± 0.3 °C SEM AL). Remarkably, we also show that inhibition of the ARC^{AgRP}→MnPO brain circuit entirely prevents fasting-induced torpor. Furthermore, we identified that both NPY and GABA are neuromodulators used by ARC^{AgRP} neurons to enable hypothermic responses during starvation. Our studies provide a detailed view of a hypothalamic pathway enabling energy conservation, a survival mechanism in conditions of low energy availability.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR103.18/CC21

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH R00 AG078903

Title: Asprosin Drives Hunger-Enhanced Memory through an Agouti-related Peptide (Agrp)-Paraventricular Nucleus of the Thalamus (PVT) Circuit

Authors: *H. XU[1], H. LIU[2], B. BASU[7], X. FANG[3], H. LIU[2], M. YU[2], L. TU[4], Y. LI[8], Q. LIU[8], Y. DENG[9], Y. YANG[8], Y. HE[5], C. WANG[6], Y. HE[10], Y. XU[11];
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Abstract: INTRODUCTION: Survival relies on the brain's ability to detect and remember threats, a capability that likely drove the evolution of specialized memory systems for retaining multiple danger cues. This ability is particularly pronounced during hunger, when the urge to seek food must outweigh predation risks.
METHODS: We developed an assay to assess how effectively mice recall two distinct threat cues linked to the same danger.
RESULTS: Hunger significantly enhances recall accuracy, with memory performance notably higher in hungry states. We identify the hunger hormone asprosin as central to this process, demonstrating its crucial role in encoding multiple threat memories. Asprosin activates the Agrp-PVT neural circuit, a pathway by which hunger dynamically enhances the brain's memory systems.
DISCUSSION: The identification of asprosin as a key regulator of threat memory advances our understanding of memory biology and suggests new therapeutic avenues for treating memory impairments by leveraging hunger-driven cognitive mechanisms.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR103.19/CC22

Topic: G.08. Food and Water Intake and Energy Balance

Support: AHA Postdoctoral Fellowship 26POST1562706

Title: An orally bioavailable Lac-Phe analog mimics exercise-induced hypophagia by inhibiting AgRP neurons

Authors: *Q. LIU, Y. XU;
Univ. of South Florida, Tampa, FL

Abstract: Exercise is a powerful intervention for reducing obesity and associated metabolic diseases. *N*-lactoyl-phenylalanine (Lac-Phe) is the most significantly elevated circulating metabolite following exercise, and pharmacological elevation of plasma Lac-Phe in mice mimics several beneficial effects of exercise, including hypophagia, weight loss, and improved glucose tolerance. These findings suggest that Lac-Phe may represent a promising anti-obesity agent. However, Lac-Phe is not stable when delivered orally and currently requires intraperitoneal administration, highlighting an urgent need to develop safe, non-invasive, and practical delivery strategies. Here, we synthesized an orally bioavailable Lac-Phe analog, YE-B, that can be administered by oral gavage. We found that acute oral administration of YE-B reduced food intake in both chow- and high-fat diet-fed mice without inducing aversive responses. Importantly, chronic YE-B treatment suppressed body weight gain and reduced fat mass, suggesting that YE-B may serve as an effective anti-obesity agent. Using ex vivo brain-slice electrophysiology, we further showed that YE-B directly inhibits agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus (ARH). Moreover, chemogenetic activation of AgRP neurons abolished YE-B-induced hypophagia, providing in vivo evidence that YE-B suppresses feeding through inhibition of AgRP neurons. Together, these findings demonstrate that oral administration of YE-B provides a more practical and patient-friendly approach than injection-based Lac-Phe delivery, supporting YE-B as a potential oral anti-obesity therapeutic candidate.

Disclosures: Q. Liu: None. **Y. Xu:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR103.20/CC23

Topic: G.08. Food and Water Intake and Energy Balance

Support: DK132673

Title: Leptin impacts on primary cilia in the ventromedial hypothalamus

Authors: *C. PETTY, E. NOBLE;
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Abstract: Leptin acts in the dorsomedial ventromedial hypothalamus (dmVMH) to reduce food intake. This process relies on the binding of leptin to its receptor (LepRb), whose presence on the cellular membrane requires intact primary ciliary signaling. Primary cilia are small hair-like appendages found on most mammalian cells which house G protein-coupled receptors (GPCRs), whose signals are transduced via adenylyl cyclase type 3 (ADCY3). Leptin increases ADCY3 loading onto primary cilia in the hypothalamus, and ADCY3 is necessary for anorexigenic responses of certain circulating neuropeptides. Whether leptin modulates ADCY3 in the dmVMH or if ADCY3 is required for the anorexigenic response of leptin in this region remains unknown. We hypothesize that leptin increases loading of ADCY3 onto primary cilia in the dmVMH and that ADCY3 in this region is necessary for leptin-mediated reductions in food intake. Sprague Dawley rats (n=8/group) were injected with a dose of leptin effective to reduce food intake and pSTAT3, a marker for LepRb activation, was elevated in the dmVMH. These findings were accompanied by an increased length and number or ADCY3+ primary cilia. shRNA-mediated virogenetic knockdown of ADCY3 in the dmVMH increased body weight and cumulative food intake (n=12/group). Since leptin in the dmVMH reduces food intake and knockdown of ADCY3 increases food intake, there may be a mechanistic link between ADCY3 and leptin signaling in this region. Our findings provide insight into understanding how the anorexigenic effects of leptin in the dmVMH may rely in part on primary cilia, and ongoing experiments will directly test this hypothesis.

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

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Program #/Poster #: PSTR103.21/CC24

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH R01DA054924
NIH P30DA048736
UW NORC pilot grant

Title: Lateral hypothalamus neurotensin neurons encode diverse features of consumption behavior

Authors: *M. C. LOVELESS[1], D. SUMARLI[1], G. DAVIS[1], K. SCHROEDER[1], S. MA[1], C. BRYAN[1], E. VU[1], M. E. SODEN[2];
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Abstract: Consummatory behaviors are governed by a wide range of factors, including internal state (i.e. hunger or thirst), motivation, arousal, reward learning, and motor execution. A

population of neurons in the lateral hypothalamus expressing the peptide neurotensin (LH-Nts neurons) has been linked to many different features of consumption, but the precise mechanism of LH-Nts control over these processes is still unclear, and whether these neurons encode specific features of consummatory action is not known. To determine the activity profile of LH-Nts during reward and consumption behaviors, we performed fiber photometry with the calcium indicator GCaMP6m in these neurons and utilized a head-fixed multispout setup to deliver solutions with varying caloric content (water, 10% and 20% sucrose, and saccharin) under food and water restriction. We found that LH-Nts neurons are activated during licking of all solutions tested, and this response is stronger during water restriction than food restriction. Linear modeling of the photometry signal revealed that the largest determinant of LH-Nts activity was lick count, with more modest contributions of internal state or solution identity. To further explore the role of LH-Nts neurons in consumption behaviors, we used expression of tetanus toxin (TeTox) to silence LH-Nts neurons and found that these mice show reduced licking on the head-fixed task in a state-dependent manner. TeTox mice also had significant reductions in fat mass, water intake, locomotor activity, and body temperature relative to controls, along with a significant increase in respiratory exchange ratio (RER) during the dark cycle, consistent with an increase in carbohydrate metabolism. Despite body weight and composition changes, silencing LH-Nts neurons did not change overall food intake. However, we found that LH-Nts neurons are activated during consumption of a solid food reward pellet in an operant task, and this response decreases across days, reflecting novelty-dependent changes in activity. Furthermore, TeTox silencing of LH-Nts impairs acquisition of operant responding, with TeTox mice earning significantly fewer sucrose rewards than control mice in training. Together, these results indicate that LH-Nts neurons contribute to diverse behavioral processes underlying consumption.

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Poster

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Topic: G.08. Food and Water Intake and Energy Balance

Support: NIDDK Grant R01-DK103808
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NIGMS Support T32-GM092715

Title: SBI-553 suppresses food intake and weight gain in hungry mice

Authors: *K. BLACK[1], J. Y. RAMIREZ[1], S. C. MILCAREK[1], N. DENNIS[1], R. BUGESCU[1], S. OLSON[2], Z. A. MCELLIGOTT[3], L. M. SLOSKY[4], G. M. LEINNINGER[1];
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[3]Psychiatry; Bowles Ctr. for Alcohol Studies, Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [4]Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: Obesity affects >40% of the U.S. population, underscoring the need for safe, effective treatments. Neurotensin suppresses feeding and promotes weight loss in rodents via neurotensin receptor 1 (NtsR1), which signals through both β-arrestin and Gq pathways. However, NtsR1 activation also induces adverse side effects such as hypothermia and hypotension (thought to be mediated by Gq signaling), which has limited the clinical potential of this ligand-receptor system. SBI-553, a novel β-arrestin-biased allosteric modulator of NtsR1, has potential to avoid these adverse effects. Published work shows that SBI-553 reduces intake of pharmacological rewards (psychostimulants, ethanol) and pain without producing the negative side effects associated with Gq signaling. We therefore hypothesized that SBI-553 would suppress intake of natural rewards (food) and promote weight loss in mice. To test this, regular-weight and diet-induced obese mice were treated with either SBI-553 (12 mg/kg, i.p.) or saline in a crossover study design. Mice underwent metabolic profiling under homeostatic conditions with *ad libitum* access to food and water as well as fasting-induced refeeding. Paired t-tests showed that under homeostatic conditions, SBI-553 acutely suppressed feeding in male obese mice ($n=7$, $p<0.05$) without altering other metabolic measures. When mice were fasted to induce hunger, SBI-553 treatment suppressed refeeding and weight gain in regular-weight ($n = 9$ males, 7 females, $p<0.05$) and obese mice ($n = 7$ males, 8 females, $p<0.01$—0.05). Together, these results suggest that SBI-553 suppresses feeding and weight gain in the face of enhanced feeding drive. In the future, SBI-553 might be useful to restrain feeding during high appetitive drive states such as dieting to support weight loss.

Disclosures: K. Black: None. **J.Y. Ramirez:** None. **S.C. Milcarek:** None. **N. Dennis:** None. **R. Bugescu:** None. **S. Olson:** None. **Z.A. McElligott:** None. **L.M. Slosky:** None. **G.M. Leinninger:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.23/CC26

Topic: G.08. Food and Water Intake and Energy Balance

Support: United States Department of Defense (HT9425-23-1-0579)
NIH (3-R01-DK103808)

Title: Does Loss of Neurotensin Expression within the Lateral Hypothalamic Area of the Brain Promote Comorbid Obesity and Pain?

Authors: *K. THOMPSON[1], I. RENDER FLORES[1], A. RESCHKE[1], R. BUGESCU[1], G. O. LAUMET[2], G. M. LEINNINGER[2];
[2]Physiol., [1]Michigan State Univ., East Lansing, MI

Abstract: There is a gap in the treatment for comorbid obesity and chronic pain, with weight loss medications not treating pain and pain medications often leading to weight gain. The central Neurotensin (Nts) system has potential to simultaneously support weight loss and analgesia. Injecting the Nts peptide into the brain reduces feeding and provides antinociception, but the endogenous sources of Nts in the brain mediating these effects are unclear. Our team has characterized Nts-expressing neurons in the lateral hypothalamic area (LHA) that, when activated, increase locomotor activity but reduce feeding, body weight and pain. However, LHA^{Nts} neurons release Nts as well as other neuropeptides such as GABA, corticotrophin releasing hormone (CRH), and galanin, yet it remains unclear if Nts vs. these other signals are critical for weight loss and analgesia. The goal of this study is to understand the necessity of LHANts in weight and pain management. We hypothesize that depleting Nts from the LHA will cause a significant increase in body weight and pain. To test this, we injected $Nts^{flox/flox}$ mice in the LHA with either an AAV-GFP (Controls with intact LHA^{Nts} neurons) or AAV-Cre-GFP virus to selectively deplete Nts expression from the LHA and not other brain regions (Nts Depleted). We then studied Control and Nts Depleted mice for effects on feeding, body weight, pain sensitivity, and dopamine-mediated behaviors while they were fed *ad libitum* chow or high-fat diet. We found that Nts Depleted mice have increased body weight on both regular chow and high-fat diet compared to Controls with intact LHA Nts expression. We also found that Nts Depleted mice have increased pain sensitivity. Moreover, Nts Depleted exhibit increased operant responding for sucrose and reduced amphetamine-induced locomotor activity; these behaviors suggest that loss of Nts from the LHA impairs the mesolimbic dopamine system that is critical for modulating motivated feeding and movement. Taken together, these data suggest that Nts expression within the LHA is important for restraining feeding and the development of obesity and comorbid pain and could be a contributor to the development of obesity-pain. Going forward, these findings could inform future design of approaches to restore or augment Nts signaling to support healthy weight. This work was supported by awards from the United States Department of Defense (HT9425-23-1-0579) and the NIH (3-R01-DK103808).

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Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.24/CC27

Topic: G.08. Food and Water Intake and Energy Balance

Support: University of Utah, Department of Neurobiology Start Up Grant

Title: Photocaged Neurotensin Analogs for Optically Gated Control of Neurotensin Receptor Signaling In Vivo

Authors: *D. E. FENG, H. A. WADSWORTH, I. AHMED;
Dept. of Neurobio., Univ. of Utah, Salt Lake City, UT

Abstract: Neurotensin (NTS) coordinates diverse physiological processes across the brain and periphery, shaping state-dependent behaviors, including feeding, pain responses, and social interaction. Conventional studies of NTS related function have primarily relied on exogenous NTS administration or optogenetic activation, followed by behavioral or physiological readouts. These approaches are limited either by insufficient temporal and spatial precision or by the inability to isolate peptide-specific effects due to co-release with other neurotransmitters. To address these limitations, we developed photocaged NTS (pcNTS) analogs that permit the delivery of functionally inert NTS and enable rapid, localized activation upon ultraviolet-light-induced uncaging. We designed and synthesized seven pcNTS analogs, each containing a photolabile protecting group installed at a specific amino acid residue within NTS or NTS (8-13). Using high-performance liquid chromatography and mass spectrometry, we confirmed that all pcNTS analogs remained stable in saline for at least 24 h in the dark. Among them, two analogs exhibited the fastest photoconversion kinetics, showing detectable uncaging within 30 s of UV exposure and clean conversion to NTS within 7 min. To identify lead analogs, we performed a G protein coupling assay measuring Gαq/11 subunit activation. Lead analogs showed at least 500-fold reduction in potency relative to NTS before photolysis and full recovery of NTS-like potency after photolysis. We next characterized uncaging kinetics in HEK293T cells using a GFP-based NTS receptor biosensor (ntsLight 2.0) and found that uncaging-induced NTSR activation occurred within 10 s of UV exposure. To evaluate its applicability in vivo, we delivered pcNTS into the nucleus accumbens and photolyzed it via bilateral optical fibers. Photolysis elicited 5-8°C reductions in body temperature that scaled with the duration of UV exposure. Ongoing studies are assessing the analog's compatibility with electrophysiological recordings, and extending its application to circuits underlying sickness behavior and torpor. Together, these studies introduce pcNTS as an optopharmacological tool for precise control of neurotensin receptor activation. This platform enables systematic dissection of how local versus volume-transmission neurotensin signaling shapes physiology and behavior.

Disclosures: D.E. Feng: None. **H.A. Wadsworth:** None. **I. Ahmed:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.25/CC28

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/NIMH grant R01MH142540
NIH/NIDA grant R01DA058653
NSF/CAREER grant 2235858

Title: Growth hormone secretagogue receptor activation modulates cost-benefit decision-making via the dorsomedial striatal circuit

Authors: *A. Y. MACIAS[1], A. SALCIDO[1], N. REYES[1], S. BATSON[1], D. BECK[4], K. NEGISHI[5], C. HEATON[1], A. GIRI[8], R. IBÁÑEZ ALCALÁ[2], L. RAKOCEVIC[2], H.-L. WANG[6], I. R. WICKERSHAM[9], Y. SHAHAM[7], T. M. MOSCHAK[3], K. GOOSENS[10], A. FRIEDMAN[11]; [1]Biol. Sciencess, [3]Biol. Sci., [2]Univ. of Texas at El Paso, El Paso, TX; [4]Biol. Sciencess, The Univ. of Texas at El Paso, El Paso, TX; [5]IRP/NIDA/NIH, BALTIMORE, MD; [7]Behavioral Neurosci. Br., [6]IRP/NIDA/NIH, Baltimore, MD; [8]Univ. of Texas at El-Paso, El-Paso, TX; [9]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [10]Dept. Psychiatry; Dept. Pharmacol. Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [11]Biological Science, UTEP, El Paso, TX

Abstract: Growth hormone secretagogue receptors (GHSRs) regulate feeding, reward processing, and cost perception, but their role in conflict decision-making remains unclear. We tested whether GHSR activation alters cost-benefit decision-making using a behavioral task battery in which rats encountered rewarding and aversive stimuli either independently or simultaneously. In non-conflict tasks, rats were presented with a single rewarding (Food or Toy) or aversive (Light) stimulus. In conflict tasks, rewarding stimuli were paired with an aversive light (Food+Light or Toy+Light), requiring animals to weigh reward against cost. Systemic administration of the GHSR agonist ibutamoren (IBU) at a dose of 2 mg/kg administered via intraperitoneal injection did not alter approach behavior in non-conflict tasks. However, IBU selectively reduced approach during conflict tasks, indicating increased behavioral sensitivity to cost during conflict decision-making. These effects were not accompanied by changes in food consumption, suggesting that altered conflict behavior was not driven by changes in hunger. A higher dose of IBU (10 mg/kg) increased food consumption but did not alter behavior in either conflict or non-conflict tasks, revealing a dose-dependent effect of GHSR activation on cost sensitivity during conflict. To determine the circuit mechanism underlying these effects, we chemogenetically manipulated striosomes in the dorsomedial striatum of Oprm1-Cre rats. Striosomal inhibition prevented IBU-induced conflict avoidance, whereas striosomal excitation reproduced the behavioral phenotype in the absence of IBU. Together, these findings suggest that GHSR activation at 2 mg/kg selectively influences decision-making when animals must choose whether to approach a reward despite an associated aversive cost, such as in the Food+Light and Toy+Light conflict conditions. The absence of this effect at 10 mg/kg indicates a dose-dependent role for GHSR signaling in conflict sensitivity and identifies striosomes as a key circuit component underlying this behavior. See related posters by Neftali Reyes, Alexis Salcido, and Lara Rakocevik (linking group: ForestSpring).

Disclosures: A.Y. Macias: None. **A. Salcido:** None. **N. Reyes:** None. **S. Batson:** None. **D. Beck:** None. **K. Negishi:** None. **C. Heaton:** None. **A. Giri:** None. **R. Ibáñez Alcalá:** None. **L. Rakocevic:** None. **H. Wang:** None. **I.R. Wickersham:** None. **Y. Shaham:** None. **T.M. Moschak:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.26/CC29

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/NIMH grant R01MH142540
NIH/NIDA grant R01DA058653
NSF/CAREER grant 2235858

Title: Dose-dependent recruitment of the striosome-LHb-dopamine circuit by GHSR activation

Authors: *N. F. REYES[1], A. A. SALCIDO[1], A. Y. MACIAS[1], S. A. BATSON[1], D. W. BECK[1], K. NEGISHI[2], C. N. HEATON[1], A. GIRI[1], L. D. DAVILA[1], R. J. IBÁÑEZ ALCALÁ[1], L. I. RAKOCEVIC[1], H.-L. WANG[2], I. R. WICKERSHAM[4], Y. SHAHAM[3], T. M. MOSCHAK[1], K. A. GOOSENS[5], A. FRIEDMAN[1];
[1]Univ. of Texas at El Paso, El Paso, TX; [3]Behavioral Neurosci. Br., [2]IRP/NIDA/NIH, Baltimore, MD; [4]McGovern Inst. for Brain Res., MIT, Cambridge, MA; [5]Dept. Psychiatry; Dept. Pharmacol. Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The gut-brain axis (GBA) regulates behavior through circulating hormones that influence neural circuit activity. Dysregulation of the hunger hormone ghrelin has been implicated in neuropsychiatric disorders characterized by altered decision-making, including substance use disorder, post-traumatic stress disorder, and major depressive disorder. Because striosomes are specialized striatal compartments implicated in these disorders, we investigated how GHSR activation influences the striosome-LHb-dopamine pathway. To test this, we first examined cFos expression across 50 brain regions following IBU administration and found that dorsomedial striosomes and the LHb exhibited the greatest increases in cFos expression. Second, dose-response studies revealed that moderate doses of IBU (1 mg/kg, 2 mg/kg) selectively increased cFos expression in striosomes, whereas a high dose (10 mg/kg) failed to alter activity in either striosomes or matrix. Third, consistent with selective GHSR expression in striosomes, a biotinylated ghrelin binding assay revealed preferential ghrelin binding within striosomes and dose-dependent receptor occupancy following IBU administration. Similar to striosomes, moderate doses of IBU increased cFos expression in the LHb and elevated pPDH expression in daSNc. Additionally, feeding behavior exhibited a distinct dose-response profile, as moderate doses of IBU (1 mg/kg, 2 mg/k) and acyl-ghrelin (4.3 μg/kg) did not alter food consumption, whereas high doses of IBU (10 mg/kg) and acyl-ghrelin (26 μg/kg) significantly increased feeding consumption. Consistent with this observation, only 10 mg/kg IBU increased cFos expression in the arcuate nucleus, a key regulator of feeding behavior. These findings support a model in which intermediate levels of GHSR activation preferentially recruit the striosome-LHb-dopamine pathway, resulting in altered downstream dopaminergic signaling. In conclusion, these data support the existence of a dose-dependent, striosome-centered mechanism through which ghrelin signaling selectively engages the striosome-LHb-dopamine pathway to influence decision-making.
See linked posters by: Andrea Macias, Alexis Salcido, and Lara Rakocevic

Disclosures: N.F. Reyes: None. **A.A. Salcido:** None. **A.Y. Macias:** None. **S.A. Batson:** None. **D.W. Beck:** None. **K. Negishi:** None. **C.N. Heaton:** None. **A. Giri:** None. **L.D. Davila:**

None. **R.J. Ibáñez Alcalá:** None. **L.I. Rakocevic:** None. **H. Wang:** None. **I.R. Wickersham:** None. **Y. Shaham:** None. **T.M. Moschak:** None. **K.A. Goosens:** None. **A. Friedman:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.27/CC30

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NDSEG Fellowship

Title: Putative Human Striosomes Underlie Decision-making Strategies

Authors: *L. RAKOCEVIC[1], C. HEATON[1], D. BECK[2], L. DAVILA[3], R. IBÁÑEZ ALCALÁ[1], K. NEGISHI[4], D. TYULMANKOV[5], K. GOOSENS[6], A. FRIEDMAN[7]; [1]Univ. of Texas at El Paso, El Paso, TX; [2]The Univ. of Texas at El Paso, Gig Harbor, WA; [3]The Univ. of Texas at El Paso, El Paso, TX; [4]IRP/NIDA/NIH, BALTIMORE, MD; [5]Electrical and Computer Engin., USC, Los Angeles, CA; [6]Dept. Psychiatry; Dept. Pharmacol. Sci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [7]Biological Science, UTEP, El Paso, TX

Abstract: In order to study decision-making strategies, it is not enough to look at decisions in isolation - instead, it is necessary to look at a series of decisions made within a single context to understand the underlying function that the decisions are outputs of. Decision-making has particular importance as a key symptom of neuropsychiatric and neurological disorders. To this end, we created a decision-making task that looks at many related but differing decisions within a single context to specifically be able to calculate the psychometric function underlying each session. We analyzed these sets of decisions and found that certain psychometric function shapes recurred across multiple contexts and people, and that most distinct sessions could be described using one of these psychometric functions, or strategies. Using a novel algorithm to identify striosomes in humans in vivo using functional analysis of the cortico-striatal-dopaminergic circuit in fMRI data, we found that putative striosomal activity corresponds to decision-making strategy which also could be explained as decision-making bias.

Disclosures: L. Rakocevic: None. **C. Heaton:** None. **D. Beck:** None. **L. Davila:** None. **R. Ibáñez Alcalá:** None. **K. Negishi:** None. **D. Tyulmankov:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.28/DD1

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/NIMH grant R01MH142540
NIH/NIDA grant R01DA058653
NSF/CAREER grant 2235858

Title: Ghrelin signaling recruits striosomal circuit to influence conflict-based decision-making

Authors: *A. SALCIDO[1], N. F. REYES[1], A. Y. MACIAS[1], S. A. BATSON[1], D. W. BECK[1], K. NEGISHI[2], C. N. HEATON[1], A. GIRI[1], L. D. DAVILA[1], R. J. IBÁÑEZ ALCALÁ[1], L. I. RAKOCEVIC[1], H.-L. WANG[2], I. R. WICKERSHAM[4], Y. SHAHAM[3], T. M. MOSCHAK[1], K. A. GOOSENS[5], A. FRIEDMAN[1];
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Abstract: Decision-making (DM) is a core cognitive process disrupted across disorders such as substance use disorder, PTSD, suicide, and Huntington's disease. Many of these conditions exhibit altered ghrelin signaling and dysfunction within striosomes, a specialized compartment of the striatum implicated in decision-making and dopamine regulation. However, whether ghrelin signaling directly influences striosomal activity to alter decision-making remains unknown. We first examined the effects of activating the growth hormone secretagogue receptor (GHSR) using Ibutamoren Mesylate (IBU), a ghrelin receptor agonist. GHSR expression was enriched within striosomes ($p=0.001$), and systemic IBU administration increased cFos expression, an immunohistochemical marker of neuronal activation, within dorsomedial striosomes ($p<0.0001$). Next, to determine whether this recruitment translated to changes in striosomal activity in vivo, we performed longitudinal calcium imaging in Oprm1-Cre rats (n=8) expressing a Cre-dependent calcium indicator to selectively target striosomes. Administration of either IBU or acyl-ghrelin increased the number of active striosomal neurons, demonstrating that both synthetic and endogenous GHSR agonists recruit a common striosomal population. Third, we used Cre-dependent DREADDs to selectively manipulate striosomal neurons in Oprm1-Cre rats (n=40). Inhibiting striosomes prevented IBU-induced behavioral changes in conflict decision-making and striosomal activation, whereas exciting striosomes reproduced these effects in the absence of IBU. Manipulating striosomal activity produced corresponding changes within the lateral habenula and dopaminergic substantia nigra pars compacta, demonstrating that striosomes are necessary and sufficient to drive the downstream circuit state associated with ghrelin signaling and decision-making. Finally, computational modeling suggests that activation of this circuit biases behavior toward cost avoidance during conflict while minimally affecting low-conflict choices. Together, these findings identify the striosome-LHb-daSNc circuit as a mechanism through which ghrelin signaling influences conflict-based decision-making.See linked posters by:
Andrea Macias, Neftali Reyes, and Lara Rakocevic

Disclosures: A. Salcido: None. **N.F. Reyes:** None. **A.Y. Macias:** None. **S.A. Batson:** None. **D.W. Beck:** None. **K. Negishi:** None. **C.N. Heaton:** None. **A. Giri:** None. **L.D. Davila:**

None. **R.J. Ibáñez Alcalá:** None. **L.I. Rakocevic:** None. **H. Wang:** None. **I.R. Wickersham:** None. **Y. Shaham:** None. **T.M. Moschak:** None. **K.A. Goosens:** None. **A. Friedman:** None.

Poster

PSTR103: Energy Balance: Anatomy, Systems, Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR103.29/DD2

Topic: G.08. Food and Water Intake and Energy Balance

Support: Max-Planck Society
European Union's Horizon 2020 research and innovation programme #885192, BrainRedesign
Fapesp #2024/09749-9
Fapesp #2024/01864-3
Fapesp #2023/02896-3

Title: PKCd^{+}neurons in the central amygdala are required for GLP1R agonist-induced hypophagia.

Authors: *S. C. MOTTA[1,2], A. M. TAMAIS[1,2], A. P. ALMEIDA[1,2], S. PAIXAO[2], R. KLEIN[2]; [1]Anat., Univ. of Sao Paulo, Inst. of Biomed. Sci., Sao Paulo, Brazil; [2]Molecules Signaling Develop., Max Planck Inst. for Biol. Intelligence, Martinsried, Germany

Abstract: Obesity is a global epidemic currently affecting >2 billion people. This presents a major burden to health systems and societies, world-wide. A new generation of anti-obesity drugs that mimic gut hormones such as GLP1 has revolutionized obesity treatment and bears great potential as therapeutics for other addiction problems. However, the brain mechanisms by which these drugs elicit their desired weight lowering effects are not well understood. The central amygdala (CeA) is known for its role in food consumption and for its neuronal heterogeneity that encompasses appetitive and aversive neuronal subpopulations. The CeA was recently shown to be activated after administration of GLP1R analogs, but the relative activities of CeA subpopulations remained mostly unclear. Here, we report that administration of GLP1R analogs such as Liraglutide and Semaglutide caused sustained activation of CeA neurons, mostly in the lateral subdivision (CeL), mainly recruiting anorexigenic PKCδ^{+} neurons. In comparison, the medial part of CeA (CeM), only showed a modest increase, with some participation of GLP1R^{+} neurons. Chemogenetic inhibition of CeA-PKCδ^{+} neurons during administration of GLP1R analogs in homeostatic and hedonic feeding assays attenuated their hypophagic effects, indicating that the activity of PKCδ^{+} neurons is required for GLP1R analogs to suppress appetite. Moreover, inhibition of PKCδ^{+} neurons prevented some of the weight loss induced by Semaglutide during hedonic feeding. In contrast, chemogenetic inhibition of GLP1R^{+} neurons in the CeA had no effect on the ability of GLP1R analogs to lower food consumption. These results suggest that CeA- PKCδ^{+} neurons are essential integrators of GLP1R analog responses in the brain.

Disclosures: S.C. Motta: None. **A.M. Tamais:** None. **A.P. Almeida:** None. **S. Paixao:** None. **R. Klein:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.01/DD3

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH Grant R01MH132795

Title: Neural Correlates of Fear Memory - Prelimbic Somatostatin-Positive Neurons and Associative Fear Memory

Authors: *M. B. DICKINSON, A. GALLAGHER, J. IQBAL, P. SHRESTHA;
Neurobio. and Behavior, State Univ. of New York Stony Brook, Stony Brook, NY

Abstract: Memory is thought to encompass a series of phases including encoding, consolidation, and recall. Various brain areas contribute to specific stages of learning and memory, engaging a distributed network involving multiple distinct areas in each stage. Associative fear memory paradigms such as Pavlovian fear conditioning serve as a model for testing memory, with relevant parallels in human disorders related to anxiety. By determining the contribution of different brain areas in associative fear memory activity we can more fully characterize the circuitry involved in learning and memory.
The prelimbic (PL) subregion of the medial prefrontal cortex has long been implicated in long-term memory recall in rodents and is increasingly recognized as a critical node in the acquisition and early consolidation of associative fear memories. Recent work indicates that inhibitory signaling within the PL is rapidly engaged following fear conditioning, suggesting that local inhibitory circuits play an active role during memory formation. Notably, somatostatin-positive (SST+) interneurons in the PL receive long-range inputs from thalamic nuclei, including the paraventricular thalamus, positioning them to regulate PL excitability during threat learning and memory storage via the inhibition of parvalbumin-positive (PV+) interneurons. We hypothesized that SST+ neurons gate inhibition within the PL during the consolidation of differential cued threat memories so we developed a novel, versatile viral chemogenetic tool (viPKR) that enables transient, cell-type-specific inhibition of protein synthesis. This Cre-dependent, drug-inducible construct expresses the kinase domain of double-stranded RNA-activated protein kinase (PKR), which phosphorylates eukaryotic initiation factor 2α (eIF2α) at Ser51 to reversibly suppress de novo translation, an approach we have previously validated in knock-in mouse models. SST-Cre mice received bilateral PL injections of viPKR and, following recovery, were trained in a differential threat conditioning paradigm requiring discrimination between threat-predictive cues of varying salience. Remote long-term memory was assessed 28 days after training. Transient inhibition of protein synthesis in PL SST+ neurons during acquisition and early consolidation resulted in a marked reduction in long-term memory fidelity. These findings demonstrate that

translational activity within prelimbic SST+ interneurons is essential for proper consolidation and long-term discrimination of threat-associated cues, supporting a central role for inhibitory microcircuits in shaping fear memory stability and generalization.

Disclosures: M.B. Dickinson: None. **A. Gallagher:** None. **J. Iqbal:** None. **P. Shrestha:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.02/DD4

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH R01MH132795
Fulbright Foreign Student Program

Title: Optimal Extinction Spacing and Infralimbic Oxytocin Signaling Promote Resistance to Fear Relapse

Authors: *S. ALBANNA[1], J. STANSIL[3], P. SHRESTHA[2];
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Abstract: Fear relapse remains a major challenge for the long-term efficacy of exposure therapy in post-traumatic stress disorder (PTSD). Although oxytocin (OT) is well known to support fear extinction, its role in preventing fear recovery after treatment is far less clear, and clinical trials have produced mixed results. Furthermore, fear reinstatement and renewal phenomena are usually studied separately, whereas in real-world contexts, patients relapse after exposure to both stressors and novel environments. To more closely model real-world conditions, we developed a behavioral paradigm that combines Pavlovian threat conditioning, two extinction sessions spaced by 10, 60, or 360 minutes, a reminder shock, and testing in a novel context. We found that spacing the first two extinction sessions by 60 minutes reduced spontaneous fear recovery at the start of the second extinction session and produced the strongest protection against later fear relapse in the novel context. Using the GRAB-OT1.9 sensor, we observed a robust surge in infralimbic oxytocin release during the early conditioned stimulus presentations that gradually declined across extinction training. Given that oxytocin receptors (OTRs) are expressed on both excitatory and inhibitory neurons in the medial prefrontal cortex, we targeted OTR-expressing interneurons. Chemogenetic manipulation of these cells prior to extinction revealed sex-specific effects on extinction learning. Moreover, OTR knockdown prior to retrieval testing increased fear expression in the novel context, and chemogenetic silencing of OTR-expressing cells similarly exacerbated fear relapse. Together, these findings indicate that strategically spaced extinction sessions generate more durable fear suppression and reveal an important role for infralimbic OTR in both fear extinction and the prevention of relapse.

Disclosures: S. Albanna: None. **J. Stansil:** None. **P. Shrestha:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.03/DD5

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH R01MH132795
T32GM148331

Title: Stress engages prefrontal ensembles to drive maladaptive avoidance via Tsc2-mTORC1 pathway

Authors: *S. LAWAL, D. SHARMA, O. TABAKA, M. MUJTABA, P. SHRESTHA;
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Abstract: Emotional regulation is essential for adapting to environmental challenges, including recognizing and responding to threats. Protein synthesis plays a central role in fear learning, memory, and emotional control, and is tightly regulated by the TSC-mTORC1 pathway. TSC proteins act as inhibitors of mTORC1, and disruptions in this pathway, such as loss-of-function mutations in Tsc1 or Tsc2, can alter protein synthesis. However, the cell-type-specific mechanisms linking disrupted protein synthesis to emotional dysregulation remain unclear. Chronic social isolation, a potent psychological stressor in social animals, can induce persistent negative emotional states and promote maladaptive avoidance behaviors associated with anxiety disorders. The medial prefrontal cortex (mPFC) is a key regulator of learned emotional responses, making it a critical site for investigating these effects. We hypothesized that selective deletion of Tsc2 in mPFC ensembles activated during social isolation would drive maladaptive anxiety-like behaviors via mTORC1 signaling. Using a mouse model, we selectively deleted Tsc2 in stress-activated mPFC ensembles and assessed behavior following prolonged isolation. This manipulation led to exaggerated avoidance behavior in a signaled active avoidance task, indicating a maladaptive threat response. These effects were specific to stress-activated ensembles rather than random mPFC neurons and were associated with somatodendritic hypertrophy, and elevated calcium signaling during behavior. Importantly, chronic treatment with mTORC1 inhibitor or Raptor knockdown rescued these behavioral and cellular changes. Together, these findings demonstrate that stress-induced dysregulation of protein synthesis in mPFC ensembles promotes maladaptive avoidance, highlighting a circuit and pathway-specific mechanism underlying anxiety-related behaviors.

Disclosures: S. Lawal: None. **D. Sharma:** None. **O. Tabaka:** None. **M. Mujtaba:** None. **P. Shrestha:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.04/DD6

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH Grant #R01 MH132795.

Title: Sex Differences In Emotional Discrimination Of Conditional Heterozygous TSC2 Mice

Authors: *A. WILSOM;
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Abstract: Tuberous Sclerosis Complex (TSC) is a neurodevelopmental disorder characterized by memory deficits, autism, epilepsy, and other neuropsychological impairments. The disorder is caused by loss-of-function mutations in the TSC1 or TSC2 genes. Recent literature have highlighted behavioral differences in the stress responses of male and female conditional heterozygous TSC mice (cHET) following isolation-based stress-inducing environments. The heterozygous deletion of TSC2 genes in oxytocin receptor cells (OTRCs) is used to replicate pathological anxiety-like behaviors found in TSC patients, in mice. These OTRCs in areas of the limbic forebrain, such as the medial prefrontal cortex (mPFC) have been shown to be critical in the stress/threat response in the brain. Previous studies established oxytocin signaling as a modulator of threat response choices following retrieval of emotional memories. However, no prior studies have used threat avoidance paradigms to analyze the sex differences of threat response in TSC mouse models, nor attempted to identify the molecular mechanisms in OTRCs of cHET mice following threat conditioning. To address this, we implemented a behavior protocol called Differential Signaled Active Avoidance (DSAA), a type of threat avoidance conditioning, to study cognitive function and emotional learning in male and female mice with conditional heterozygous TSC2 deletion compared to wildtype controls. Additionally, we utilized immunohistochemistry to measure nascent protein synthesis that occurred in the prefrontal oxytocin receptor cells following DSAA learning and retrieval.

Disclosures: A. Wilsom: None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.05/DD7

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH R01-MH132795

Title: A prelimbic molecular clock of protein synthesis for memory persistence

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Abstract: Emotionally salient associative memories can endure for long periods, yet the mechanisms that determine their long-term stability remain unclear. Here we show that the prelimbic (PL) cortex integrates temporally structured translational programs to control both the consolidation and reconsolidation of cued threat memories. Using Pavlovian threat conditioning with in vivo fiber photometry, we found that PL calcium dynamics tightly track memory strength: discrete threat-predictive cues evoked robust activity during recent and single-timepoint remote retrieval, whereas prior retrieval selectively weakened remote expression, independent of contextual influences. Translational profiling of PL Camk2a^{+} cells uncovered a biphasic consolidation program, with an early phase characterized by ER stress-linked translational repression and robust oligodendrocyte plasticity, followed by a delayed phase engaging synaptic growth pathways. Loss- and gain-of-function approaches demonstrated that eIF2α-regulated, cap-independent translation is essential for recent consolidation and for the enduring stabilization of remote memory, whereas retrieval-induced destabilization engages a mechanistically distinct, eIF4E-dependent translational pathway required for reconsolidation. These findings identify the PL cortex as a dynamic node in which discrete modes of translational control govern the long-term persistence of emotional memories.

Disclosures: P. Shrestha: None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.06/DD8

Topic: H.01. Fear and Aversive Learning and Memory

Title: Infralimbic cortex 5-HT1A, 5-HT2A, and BDNF/TrkB signaling mediate ayahuasca-induced facilitation of aversive memory extinction

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Abstract: Extinction of aversive memories depends on plasticity in the infralimbic (IL) cortex, and impaired extinction contributes to trauma-related disorders marked by persistent, generalized aversive memories. Ayahuasca (AYA), a brew containing the serotonergic psychedelic *N,N*-dimethyltryptamine (DMT), enhances fear extinction in rats, but the underlying mechanisms and effects on traumatic-like memories remain unclear. We investigated whether AYA facilitates the

extinction of moderate and intense contextual aversive memories via IL serotonin (5-HT)1A and 5-HT2A receptors and via brain-derived neurotrophic factor (BDNF)/TrkB signaling in adult male and female Wistar rats (n=7-10/group). Rats were fear-conditioned with moderate (1.0 mA) or high-intensity (1.3 mA) footshocks, the latter producing stronger, generalized, and extinction-resistant aversive memories. Animals received repeated oral administration of vehicle or AYA (0.3 mg/kg of DMT) paired with extinction sessions on two consecutive days. Freezing was assessed during extinction acquisition, extinction retention, and generalization tests. To investigate mechanisms, rats received bilateral intra-IL infusions of the 5-HT1A antagonist WAY-100635, the 5-HT2A antagonist MDL 11,939, an anti-BDNF antibody, or the TrkB antagonist ANA-12 combined with AYA. Data were analyzed using analysis of variance (ANOVA) followed by Newman-Keuls post hoc tests. Repeated AYA treatment reduced freezing during extinction acquisition and retention in both sexes ($p \leq 0.02$) and reduced generalized fear induced by high-intensity conditioning ($p \leq 0.001$). Intra-IL blockade of 5-HT1A, 5-HT2A, or TrkB receptors prevented AYA-induced facilitation of extinction. Intra-IL anti-BDNF infusions abolished the effects of AYA on extinction retention in both sexes. During generalization testing, BDNF blockade prevented AYA-induced reductions in generalized fear in males, but not females, suggesting sex-specific BDNF-dependent regulation of generalized fear. These findings demonstrate that AYA can facilitate the extinction of aversive memories through convergent IL cortex serotonergic and BDNF/TrkB-dependent mechanisms, supporting the translational potential of AYA-assisted extinction-based interventions for trauma-related disorders.

Disclosures: I. Werle: None. **F.S. Guimaraes:** None. **R. Dos santos:** None. **J. Hallak:** None. **L.J. Bertoglio:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.07/DD9

Topic: H.01. Fear and Aversive Learning and Memory

Title: Inhibition of stress activated neurons in the basolateral amygdala reduces reactivity to new stressors

Authors: *P. MARTINEZ GONZALEZ[1,2], R. AUKEMA[1,2], E. KELKAR[3,2], C. KLENGEL[2], K. J. RESSLER[4];
[1]Depression & Anxiety, [2]McLean Hosp., Belmont, MA; [3]Northeastern Univ., Boston, MA; [4]Harvard Med. Sch., McLean Hosp. / Harvard Med. Sch., Belmont, MA

Abstract: Post-traumatic stress disorder is a highly debilitating condition characterized by the formation of persistent fearful memories after traumatic stressors and hyper-reactivity to new stress. However, the mechanisms underlying how trauma may affect future behavior, and whether this differs by trauma subtype, remains unknown. We investigated whether stress-

activated neurons in the basolateral amygdala (BLA) functionally contribute to avoidance or fear-like responses to new, contextually distinct stressors, and whether this differs by stressor subtype. Male and female transgenic TRAP2 mice were injected bilaterally within the BLA with viruses containing inhibitory hM4Di or control mCherry DREADDs. One week later, 4-hydroxytamoxifen was administered following stress to drive expression of DREADDs selectively in no trauma, shock, or restraint-activated neurons. The “no trauma” control group was exposed to a non-aversive, but novel context. We then assessed the role of “shock”, “restraint”, or “no trauma” -labeled populations by selectively inhibiting each population during a variety of behavioral tests such as open field, elevated plus maze, and fear conditioning of a new memory. Prior to each of these behavioral tests, animals were injected with deschloroclozapine (DCZ, 0.1 mg/kg, i.p.) to drive selective inhibition of either “shock”, “restraint”, or “no trauma” BLA neurons. Inhibition of “No Trauma” neurons had no effect on any behavioral test. In contrast, “shock” and “restraint” neurons displayed a stressor-dependent influence on behavior. Inhibition of BLA “shock” neurons increased ambulation during the elevated plus maze, and inhibition of “restraint” neurons decreased the time spent in the border of the open field and increases distance travelled. This suggests that both stress populations commonly alter exploratory behavior in a novel context, with “shock neurons” having a specific impact on locomotor activity. Markedly, inhibition of BLA “shock” neurons reduced freezing (an index of fear in mice) during recall of a new fear memory. In comparison, inhibition of BLA “restraint” neurons had no effect during recall of a new fear memory. Together, this elucidates potential functionally distinct neuronal populations active during different types of stress, with “restraint neurons” affecting avoidance behaviors and “shock neurons” affecting freezing behaviors. Ongoing work includes mapping projections from stress neurons through whole brain immuno-tracing as well as identifying the molecular identity of the neurons through sequencing.

Disclosures: P. Martinez Gonzalez: None. **R. Aukema:** None. **E. Kelkar:** None. **C. Klengel:** None. **K.J. Ressler:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.08/DD10

Topic: H.01. Fear and Aversive Learning and Memory

Support: Center for Study of Traumatic Stress

Title: Second-order contextual threat conditioning in dorsolateral amygdala

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Abstract: Second-order contextual conditioning is a form of higher-order learning in which a new context acquires associative value through its relationship with an established conditioned stimulus (CS) rather than through direct pairing with the unconditioned stimulus (US). It provides a useful model for understanding how complex, real-world associative networks form, as new environments may gain meaning indirectly through association with predictive cues. This process is clinically important because indirect contextual associations may contribute to persistent threat responding, including hypervigilance, and maladaptive responses in Post Traumatic Stress Disorder (PTSD). We designed a second-order Pavlovian threat conditioning protocol in Sprague-Dawley rats and mapped the distribution of phosphorylated ERK (pERK) expressing neurons in the dorsolateral amygdala (LAd) at fine-scale resolution to visualize the topography of interlinked old and new associative fear memory traces. Spatial analyses revealed a stable LAd neuronal ensemble with topographic features overlapping for both first- and second-order threat memory phases. There was one site identified, localized to the superior LAd that held a high number of neurons specific for both memory phases. We also uncovered a new site containing a small but significant number of neurons activated only after memory retrieval, suggesting these neurons may be involved in encoding the new second-order context memory. This new site was localized in the inferior LAd. The quantity of neurons activated after first- and second-order fear conditioning was not detectably different, suggesting that linking new information may not significantly add to the initial size of the original threat memory network, but rather reorganizes it. Together, these data provide the first detailed topographic measures of a second-order contextual threat memory trace in the LAd and suggest that interlinked old and new threat memories are anatomically dissociated at the level of an amygdala neuronal ensemble.

Disclosures: H.C. Bergstrom: None. **L.R. Johnson:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.09/DD11

Topic: H.01. Fear and Aversive Learning and Memory

Support: T32NS061788
R01MH139795
R01MH123768

Title: Estrous cycle regulation of negative valence neurons in basolateral amygdala during threat memory processing

Authors: *A. J. TELLEZ[1], B. HARDIN[1], P. TERAVSKIS[1], N. E. BAUMGARTNER[2], E. K. LUCAS[2];
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Abstract: Across species, the basolateral amygdala (BLA) drives the encoding and retrieval of cued threat memory. While the BLA is highly influenced by fluctuations in ovarian hormones, little is known about how neuronal activity changes across the estrous cycle to shape threat memory. In males, BLA principal neurons expressing R-spondin-2 ($Rspo2^{PN}$) are necessary and sufficient for threat memory encoding, while GABAergic interneurons expressing parvalbumin (PV^{IN}) and somatostatin (SOM^{IN}) modulate threat memory dynamics through local inhibition of principal neurons. Our single nucleus sequencing data reveal exclusive enrichment of estrogen receptor beta (ERβ) in $Rspo2^{PN}$ and, to a lesser extent, SOM^{IN} in the BLA. Given the known role of ERβ in BLA plasticity, we hypothesize that regulation of ERβ-expressing BLA microcircuitry is the underlying driver of sex differences in threat memory processing through the differential recruitment of $Rspo2^{PN}$, SOM^{IN}, and PV^{IN}. Using mouse as the model species, we combined auditory threat conditioning with fiber photometry to quantify the contributions of BLA $Rspo2^{PN}$, SOM^{IN}, and PV^{IN} in the expression and maintenance of threat memories. Subjects received bilateral infusions of adeno-associated virus in the BLA to confer expression of Ca^{2+} biosensor GCaMP6f and optic fiber implants During acquisition, all three cells types are recruited to both the conditioned stimulus (CS; auditory tone) and unconditioned stimulus (US; footshock) with distinct activity profiles. $Rspo2^{PN}$ and PV^{IN} exhibit robust initial responses to the US, to a greater degree than SOM^{IN}, with PV^{IN} recruitment decreasing across learning. Conversely, SOM^{IN} displayed a greater rate of change to the US (versus $Rspo2^{PN}$ and PV^{IN}) and increased recruitment across threat memory acquisition. We report the first observation of females engaging $Rspo2^{PN}$ across threat memory processing and provide novel evidence revealing ovarian hormone modulation of this population during threat memory acquisition, whereby $Rspo2^{PN}$ recruitment to both the CS and US is significantly less in proestrus than diestrus females or males. Unexpectedly, PV^{IN} demonstrate a sex difference in which there is greater overall recruitment to the CS and a more negative rate of change to the US in females than males. During threat memory retrieval, all three cell types are reengaged to the CS, independent of sex or ovarian hormone status. Our research highlights the contributions of sex and hormone status in threat response, with growing evidence for circulating ovarian hormones driving differences in amygdala regulation.

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Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Title: Effects of social buffering of fear on lateral to centrolateral amygdala oxytocin receptor-defined neurons in rats

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Abstract: Social buffering of fear (SBF) reduces conditioned freezing in the presence of a conspecific and can induce persistent attenuation of fear expression. We previously found in vivo that SBF in rats involves oxytocin-dependent mechanisms in the central amygdala, suggesting that social experience can remodel fear-related amygdala circuits (Hegoburu et al., Nat. Commun. 2024). However, how SBF modifies lateral amygdala (LA) fear engrams and their downstream connectivity onto defined centrolateral amygdala (CeL) neuronal populations remains unknown. We hypothesize that fear memory recall and SBF recruit distinct LA pyramidal cell ensembles that differentially engage CeL neuronal populations. Specifically, fear conditioning strengthens LA fear-engram outputs onto CeL oxytocin receptor negative (OTR^-) neurons, whereas SBF may recruit or remodel LA ensembles projecting onto CeL oxytocin receptor positive (OTR^+) neurons to reduce fear expression. To test this, adult OTR-Cre rats undergo auditory fear conditioning followed by memory recall either alone or during SBF with a naïve conspecific. LA neurons activated during fear recall or SBF are labelled using activity-dependent viral tagging, while CeL OTR^+ neurons are identified by Cre-dependent viral reporter expression. This approach allows comparison of LA fear- and SBF-associated ensembles and their synaptic targeting of CeL OTR^+ versus $OTR^–$ neurons. We quantified behavioural freezing during recall and retention and assessed c-Fos expression by histological analysis. In addition, ex vivo slice electrophysiology is used to test whether LA outputs differentially drive CeL OTR^+ and OTR^- neurons. As preliminary evidence, c-Fos immunostaining combined with Cre-dependent viral labelling in our OTR-Cre rat line revealed co-labelling of CeL OTR^+ neurons after the SBF retention test whereas fear recall alone, without SBF, produced segregated c-Fos and OTR^+ labelling. This suggests that CeL OTR^+ neurons are preferentially recruited following social modulation of fear (n=8 rats). In parallel, whole-cell patch-clamp recordings from CeL OTR^+ neurons in acute brain slices, combined with ChR2 expression in LA neurons, showed light-evoked responses in CeL OTR^+ neurons confirming functional LA to CeL connectivity onto this oxytocin receptor-defined population (n=11 cells). By combining both approaches, we can support the hypothesis that SBF engages CeL OTR^+ neurons and may redirect LA to CeL communication toward circuits that attenuates fear expression.

Disclosures: D. Caseiro: None. **R. Niu:** None. **E. Van den Burg:** None. **R. Stoop:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.11/DD13

Topic: H.01. Fear and Aversive Learning and Memory

Title: H3K27ac and HDAC2 Dynamics Associated With the Memory-Linking Window in Hippocampal Engram Neurons

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Abstract: Memory linking allows the brain to associate experiences occurring within a limited temporal window, yet the molecular mechanisms controlling this process remain unclear. Because memory linking depends on overlapping hippocampal engram ensembles, neurons encoding memories may transiently enter a plasticity-permissive state before returning to a transcriptionally restricted state. Epigenetic regulation may underlie this transition. Here, we examined whether changes in H3K27ac, a histone modification associated with active chromatin, and HDAC2, a histone deacetylase linked to transcriptional repression, are associated with the opening and closing of the memory-linking window after contextual fear conditioning. Hippocampal tissue was collected from home cage controls and from animals sacrificed 2 h, 48 h, or 96 h after contextual fear conditioning. H3K27ac and HDAC2 were assessed in adjacent hippocampal sections when possible, although final sample sizes differed because of tissue and image availability. Confocal images were acquired along the dentate gyrus, and GFP+ and GFP− neurons were quantified using QuPath. H3K27ac was analyzed in HC n=1, 2 h n=2, 48 h n=2, and 96 h n=1 biological samples, while HDAC2 was analyzed in HC n=2, 2 h n=2, 48 h n=3, and 96 h n=2. Two to four dentate gyrus images were quantified per animal, with animal number treated as the biological sample size. Data were analyzed using two-way ANOVA followed by Tukey post-hoc tests.
H3K27ac increased in GFP+ hippocampal engram neurons 2 h after conditioning and decreased at later time points, consistent with transient chromatin accessibility during the open memory-linking window. In contrast, HDAC2 showed an opposing temporal profile, increasing after the window had closed. These findings suggest that the balance between H3K27ac and HDAC2 may help define the temporal boundaries of memory linking.No se que título tenía sino ponle algo como:H3K27ac and HDAC2 Dynamics Associated With the Memory-Linking Window in Hippocampal Engram Neurons

Disclosures: M. Trejo Valencia: None. **C. Sierra:** None. **J. Graff:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.12/DD14

Topic: H.01. Fear and Aversive Learning and Memory

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Title: Effects of Medial Prefrontal TMS on Fear Memory: cTBS Enhances Fear Expression and Impairs Extinction in Mice

Authors: *H. LEE[1], S. PARK[2], Y. HUH[3], J. CHO[1];
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Abstract: The medial prefrontal cortex (mPFC), particularly its prelimbic region, is critically involved in the regulation of conditioned fear expression, whereas extinction of fear memory depends on coordinated modulation of prefrontal-amygdala circuits. Continuous theta-burst stimulation (cTBS), a patterned form of transcranial magnetic stimulation (TMS), is generally considered to reduce cortical excitability and has been proposed to engage inhibitory circuit mechanisms. Based on this inhibitory profile, we hypothesized that cTBS applied over the mPFC would suppress fear expression and facilitate the reduction of conditioned fear responses. The current study examined the behavioral effects of mPFC-targeted cTBS using a mouse auditory fear conditioning model. TMS coils were positioned over the mPFC, and mice were assigned to sham or TMS groups receiving cTBS. Behavioral assessments included the open field test (OFT) and an auditory fear conditioning paradigm consisting of fear conditioning, a 24-h auditory cue test, two extinction sessions, and long-term retention tests conducted at 72 h and 1 week after conditioning. TMS was applied for 10 min immediately after both the conditioning session and the first extinction session. In the OFT, no significant group differences were observed in locomotor activity or center/border ratio, suggesting that the cTBS did not markedly alter basal anxiety-like behavior or motor function. However, contrary to our initial hypothesis, mice receiving cTBS showed significantly higher freezing during extinction than the other groups. Although no significant group difference was detected in the initial 24-h cue test, the cTBS group showed increased freezing tendency. In the retention tests, the cTBS group exhibited significantly elevated freezing at 72 h, but this difference was not maintained at 1 week. These results suggest that cTBS applied to the mPFC can impair fear extinction and transiently enhance fear-related freezing responses. Together, these findings suggest that targeting the mPFC, particularly the prelimbic region, with cTBS does not necessarily lead to reduced fear expression despite its presumed inhibitory profile. This unexpected effect may arise from limited target specificity, as stimulation could recruit regions beyond the intended prelimbic target. Future cFos-based studies comparing regional activation patterns may help clarify the neural basis of this behavioral outcome.

Disclosures: H. Lee: None. **S. Park:** None. **Y. Huh:** None. **J. Cho:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.13/DD15

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH P20GM103449
NIH 1 R15 GM132937-01

Title: Fine Behavioral Characterization of Drosophila melanogaster With Altered NinaA Expression During Memory Formation

Authors: C. SILVERMAN, W. BECKERMAN, *A. CROCKER;
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Abstract: The detection, learning, and recall of pain are crucial to the survival of all animals. Dysregulation of these functions contributes to a number of disorders, including chronic pain, post-traumatic stress disorder, and neuropathic pain, to name a few. Here we characterize the role of the *NinaA* gene. *Drosophila Melanogaster* with mutations in *NinaA*, previously characterized for its role as a rhodopsin chaperone protein, exhibits a deficit in shock avoidance when given the opportunity to enter a safe zone in a circular arena. It is unknown where in the sensory, memory, or motor output pathways this deficit originates. We hypothesize that mutations in *NinaA* will produce learning deficits in aversive odor learning using electric shock classical conditioning. Further, if NinaA functions as a learning mutant, we hypothesize they will show impaired learning behaviors similar to those exhibited by known learning mutants. If instead NinaA functions as a nociceptive mutation, we hypothesize they will still show some learning but exhibit behaviors more characteristic of nociceptive mutants. To test this, we used a single-fly learning assay developed in our lab based on a classical T-maze, allowing us to use high-frame rate videos during conditioning, short-term memory and long-term memory tests. Videos were analyzed for avoidance of the shock-associated odor after training (indicating memory), total distance traveled, maximum velocity, grooming, freezing, and flipping. We used the following genotypes: wild-type Canton S (CS), *NinaA* mutant (in 2 different genetic backgrounds), *Phosphodiesterase 4* (*Pde4* or *Dunce*) learning mutant, and *painless* nociceptive mutant. Looking at both males and females, we find *NinaA* mutants show short-term aversive learning deficits and behavioral phenotypes more similar to *Pde4* learning mutants than to wildtype flies or painless sensory mutants. These results point to a role for *NinaA* in the short-term memory pathway, though further studies are needed to establish where it interacts and with which proteins. In this study, we outline a set of parameters to probe sensory perception and behavioral expression of learning and memory using single-fly high speed video tracking and behavioral analysis.

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Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.14/DD16

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant (RO1NS106915)
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Title: Increasing Cerebellar Endocannabinoid Tone Blocks Stress-Enhanced Fear Consolidation

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Abstract: The cerebellum is increasingly recognized as a vital structure for regulating emotion and cognition. Our laboratory previously showed that fear conditioning requires a reduction in cerebellar 2-arachidonoylglycerol (2-AG) levels. Building on this, we hypothesize that stress reduces endocannabinoid (eCB) signaling to enhance the formation of fear memories. Our results show that stress triggers a loss of cerebellar tonic eCB signaling. We found that this deficit was not caused by receptor dysfunction, since the CB1 agonist WIN55212-2 effectively suppressed miniature inhibitory postsynaptic current frequency across both stressed and naive cohorts. To investigate how stress reduces eCB signaling, we examined 2-AG regulatory enzymes. The activity of the 2- AG degrading enzyme -monoacylglycerol lipase (MAGL) remained unaffected by stress. In contrast, predator odor stress markedly decreased the level of 2-AG synthesizing enzyme -diacylglycerol lipase (DAGL). This decline in the 2-AG synthesizing enzyme occurred specifically within cerebellar lobules 5/6 that are required for associative fear memory formation. To test the behavioral consequence of stress-induced decrease in eCB signaling, mice were exposed to stress three hours before fear conditioning and were tested for memory retention the following day. These mice displayed greater freezing response to tone compared to fear conditioning alone, suggesting amplified fear memory. Systemic administration of the CB1 agonist ACEA 30 min after stress was able to block this memory enhancement. We next determined whether eCB release from cerebellar Purkinje cells was sufficient to prevent the stress-induced fear memory enhancement. We used transgenic mice that selectively express Gq-coupled DREADDs in cerebellar Purkinje cells, as activating this pathway using J60 facilitates the production of 2-AG. Importantly, injecting J60 (i.p.) 30 minutes after stress to increase 2-AG production prevented fear memory potentiation. These findings demonstrate that stress-induced deficits in cerebellar 2-AG synthesis drive the enhanced fear memory formation. Therefore, therapeutic interventions capable of restoring cerebellar endocannabinoid tone may prove highly effective in preventing the formation of traumatic memories in stress-related disorders.

Disclosures: M. Sayed: None. **C.J. Dubois:** None. **J. Fawctt-Patel:** None. **M.A. Farooq:** None. **J. Liu:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.15/DD17

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Predoctoral training grant T32 NS082145

Title: Light-Shock Association for Fear-Potentiated Startle Preserved After Chronic Unpredictable Stress

Authors: *E. KARPMAN[1], F. R. CARRENO[2], D. A. MORILAK[3];
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Abstract: Criterion E symptoms of Posttraumatic Stress Disorder (PTSD) include hypervigilance, irritability, and elevated startle reflex. However, baseline startle is not consistently elevated across clinical or preclinical studies. Rather, fear-potentiated startle (FPS), or startle reflex potentiated by a fear-associated cue, is consistently heightened in PTSD and may better capture the underlying mechanisms of this dimension of illness. Notably, potentiated startle responses remain insufficiently targeted with currently available treatments. This study aims to establish and validate an FPS paradigm integrating the CUS protocol (CUS-FPS) that is suitable for testing extinction-based interventions for PTSD in rats.Previous FPS protocols involve conditioning the rats (acquisition phase) 1-2 days prior to testing. Because this study will add CUS to the protocol, we first assessed whether conditioned fear associations are retained over the extended time course required for CUS exposure (2 weeks for males, 3 weeks for females). Three cohorts were tested: (1) rats trained on a light-shock association and tested on FPS 2-3 weeks later, (2) rats trained on both tone-shock and light-shock associations and tested 2-3 weeks later, and (3) rats trained on both associations followed by 2-3 weeks of CUS, extinction learning to the tone cue, then FPS testing with the light cue. Across all groups, startle responses were significantly greater during light cue-present trials, indicating robust retention of the conditioned fear association. Taken together, these findings validate a longitudinal CUS-FPS paradigm, demonstrating that conditioned fear memories persist despite prolonged intervals and chronic stress exposure, and that tone conditioning to implement extinction as an intervention does not interfere with startle potentiation by a conditioned light cue, providing a robust platform to investigate PTSD-relevant fear dysregulation and to evaluate novel therapeutic interventions.

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Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR104.16/DD18

Topic: H.01. Fear and Aversive Learning and Memory

Title: Memory is appended, not overwritten: a neural model of fear extinction, renewal, and the fragile Monfils-Schiller effect

Authors: *Z. BEN HOUIDI[1], S. J. GERSHMAN[2];
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Abstract: The latent cause theory of memory modification offers a computational account of how the brain decides whether to update an existing memory or form a new one, but does not specify the neural mechanisms that implement this inference. We propose Reuse-and-Append Memory (RAM), a set of mechanistic principles that reach the same goal through sparse neural coding, Hebbian learning, and pattern-matching dynamics. Neurons encoding prior experiences are automatically reactivated by similar stimuli (reuse), while uncommitted neurons are recruited to encode genuinely novel aspects of each experience, including the passage of time, binding each into an episode (append).
We formalize these principles, ground each component in published neural evidence, and establish a structural parallel with latent cause theory. We then instantiate the principles as a computational model and simulate Pavlovian fear conditioning. Using a standard conditioned stimulus (CS) and unconditioned stimulus (US) protocol, with overnight gaps as offline rehearsal periods, the model was tested on five phenomena: acquisition, extinction, renewal, spontaneous recovery, and the Monfils-Schiller timing effect. Each trial yields activations of two mutually inhibiting Fear and No-Fear populations; the larger activation sets the outcome, and their difference (the margin) measures how decisively the competition resolves. The model produced the correct outcome for all five phenomena (margins +1.5 to +4.7) across wide parameter ranges, and did so without ever modifying an existing memory: the most stable configuration was to always append and never overwrite, while enabling reconsolidation only narrowed the working regime. Even the Monfils-Schiller effect, the phenomenon most often attributed to reconsolidation, emerged this way: through a bridging event that carries safety across contexts via offline co-retrieval. The model further predicts it to be inherently fragile and replay-dependent, consistent with the mixed empirical record.
By committing to a neural mechanism, RAM separates what is typically modeled as a single prediction-error signal into two independent signals: an immediate novelty signal arising from the recruitment of new neurons that creates the memory, and a later outcome-mismatch signal that activates safety circuits when an expected outcome fails to arrive. RAM also explains representational drift through the same dynamics: frequently reused features are repeatedly stabilized, while rarely rehearsed ones decay and are reallocated to encode new content, predicting that the rate of drift scales inversely with how often a representation is reused.

Disclosures: Z. Ben houidi: None. **S.J. Gershman:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.17/DD19

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH - R15 MH129932-01 to C. Reich

Title: Revisiting the Renewal Effect in Contextual Fear Conditioning

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Abstract: The renewal effect occurs after the extinction of a conditioned fear response. It involves the sudden return of that behavior when returned to the initial fear-associated context. Previous studies have predominantly used tone-shock pairings for studying the renewal effect, however, the effectiveness of a primarily contextual-based fear conditioning protocol to elicit the same response is unclear. The present study is systematically investigating the presence of the renewal effect in contextual-fear-conditioning. Adolescent Sprague-Dawley male rats are subjected to a four-day fear acquisition, extinction, and renewal protocol. During acquisition, animals receive conditioning in a distinct context. Extinction occurs in a separate context characterized by altered visual, tactile, and olfactory cues. On the renewal test day, rats are returned to the original acquisition context to assess the recovery of conditioned fear. Separate pilot experiments are manipulating individual variables such as number of exposed shocks, amount of extinction-context exposure and contextual cues to assess optimal conditions for renewal expression. Pilot studies have sample sizes that are $n \geq 6$. Our initial observations suggest that exposure to six footshocks compared to three (0.8 mA, 2 sec, spaced 1 min apart) during the acquisition period produces more freezing during the first recall/extinction session. We also observe that ten minute recall/extinction sessions promotes smaller and more observable extinction during these trials compared to twenty-minute recall/extinction sessions. Through manipulating both the number of footshocks and the timing of recall/extinction trials, our data provide preliminary evidence of contextual-fear renewal. These studies are ongoing and will include comparisons to hippocampal-dependent cued, trace fear conditioning.

Disclosures: F. Miyashiro: None. **V. Flores:** None. **C. Maroun:** None. **A. Adawi:** None. **F. Carrillo:** None. **M. Botros:** None. **O. Ha:** None. **C.G. Reich:** None.

Poster

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Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

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Topic: H.01. Fear and Aversive Learning and Memory

Support: New Jersey Commission on Brain Injury Research Fellowship CBIR24FEL007
Veterans Affairs Merit Grant VA - I01BX004561-01A2

Title: Developing a Novel Model of Negative Urgency Using Operant Avoidance and Autonomic Arousal

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Abstract: Impulsivity is a complex behavioral trait that can be expressed in a wide variety of actions and in various conditions. Negative urgency (NU) is a dimension of impulsivity that describes acting rashly when experiencing negative affect. As a negative emotional state is imperative to the expression of NU, it has historically been studied in the context of addiction. Indeed, one of the very few animal models of NU reflects this: omission of an expected positive reinforcer induces negative affect and consequently impulsivity. However, NU can be expressed in other circumstances that are not represented in the above model. Our lab has developed a novel model of NU that uses negative reinforcement. Here, we describe our attempt to validate the model using heart rate as a measure of arousal. Male and female Sprague-Dawley rats acquired a lever-press escape-avoid paradigm reinforced by aversive foot shock. A cohort of rodents were then implanted with a chronic, in-dwelling device that recorded electrocardiogram (ECG) data. After recovery, animals completed the *unexpected cue persistence* (UCP) task where the behavior did not immediately lead to the expected termination of the cue light and tone (unexpectedly omitted). The UCP task was completed 2 weeks, 1 month, and 3 months post-implantation. Results from this experiment suggest heart rate in both sexes failed to change in response to omission trials. Females demonstrated elevated heart rate during the first trial period of a session while males did not show this aroused state. In addition, average heart rate among females decreased within session while for males it remained stable. A second cohort of rodents were used to determine if mild traumatic brain injury (mTBI) alters NU as reflected by the UCP task. Lateral fluid percussion was the mTBI model. The UCP task was completed 2 weeks and 1-month post-injury, then, all rodents were implanted with the ECG-recording device before testing at 3 months and 6 months post-injury. Preliminary results suggest injured female rodents exhibited greater non-reinforced lever pressing compared to males. How this is reflected in autonomic arousal is being investigated. Taken together, the above findings demonstrate sex differences in autonomic arousal in the UCP task prior to the addition of the injury and should be considered when exploring sex differences in NU as a result of TBI.

Disclosures: V.A. Stiritz: None. **D.Y. Bank:** None. **L.E. Paulino:** None. **X. Agbolou:** None. **K.D. Beck:** None.

Poster

PSTR104: Neurobiology of Fear and Avoidance Learning and Memory I

Location: WCC Halls A-C

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Program #/Poster #: PSTR104.19/DD21

Topic: H.01. Fear and Aversive Learning and Memory

Support: Beatrice H. Barrett Endowment for Research in Neuro-Operant Relations

Title: A Closed-Loop Adaptive Psychophysiological Procedure for Modifying Stimulus Intensity or Valence

Authors: *J. T. NGUYEN, A. BECKER, D. ORTU;
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Abstract: Cue reactivity refers to a phenomenon during which an individual experiences heightened emotional and behavioral responses in the presence of certain stimuli, and is important in various psychiatric disorders such as addiction, post-traumatic stress disorder, and phobias. Traditional classical conditioning techniques to change cue reactivity do not consistently attenuate or switch stimulus valence (appetitive/aversive) and may only produce coping (i.e., reactive behaviors to manage stress in aversive situations). Operant conditioning offers a promising alternative to changing or attenuating the aversiveness of a stimulus; yet it remains relatively unexplored. Constructional Fear Treatment (CFT) uses the contingent removal of an aversive stimulus (i.e., negative reinforcement) to teach calm, low-arousal behaviors in response to fearful stimuli. Previous research on CFT demonstrated that the procedure may result in a stimulus valence changeover, or a shift from escape/avoidance to spontaneous approach toward a previously aversive stimulus. The present study developed and evaluated a closed-loop, adaptive psychophysiological implementation of CFT in the absence of appetitive consequences and examined changes across behavioral, physiological, and neural aspects of fear responding. Individuals with arachnophobia completed CFT and pre- and post-treatment assessments. Dependent variables included Spider Phobia Questionnaire (SPQ) scores, Fear of Spiders Questionnaire (FSQ) scores, a choice-based stimulus function assessment, Galvanic Skin Response (GSR), Electroencephalography (EEG) Event-Related Potentials (ERPs), and Heart Rate Variability (HRV). During treatment, real-time GSRs contingently controlled stimulus presentation. An adaptive algorithm automatically modified stimulus size, duration, and treatment progression parameters based on trial-by-trial GSR responding. Results to date indicate differential impact on dependent variables. These preliminary findings suggest that reductions in subjective, physiological, and neural aspects of fear may occur in the absence of appetitive consequences, although additional data are needed to determine whether such changes are accompanied by stimulus valence changeover.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.01/DD22

Topic: H.01. Fear and Aversive Learning and Memory

Support: DA052108

Title: High Gamma (80 Hz) Transcranial Alternating Current Stimulation of the Infralimbic Cortex to Nucleus Accumbens Shell Pathway Alters Learned and Innate Aversion Differentially Across Sex

Authors: *E. GRABLIN[1], R. M. CARELLI[2];
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Abstract: Dysregulation of affective processing is common in psychiatric conditions such as depression and substance use disorders. The infralimbic cortex (IL) to nucleus accumbens shell (NAcSh) pathway has been implicated in affective processing in rodents. Our lab has previously shown a significant change in high gamma (80 Hz) local field potential (LFP) activity in this pathway in female but not male rats during learned negative affect (conditioned taste aversion, CTA) and innate (quinine) aversion (Douton and Carelli, 2023). Further, 80 Hz optogenetic stimulation of the IL-NAcSh pathway is causally linked to innate but not learned aversion in females (Grablin et al., 2025). Here, we examined the effects of a more translationally relevant brain stimulation method on conditioned and innate aversion in rats, namely transcranial alternating current stimulation (tACS), a form of noninvasive brain stimulation. The goal was to examine if 80 Hz tACS, that acts more globally on brain activity compared to optogenetics, can alter negative affect during CTA and quinine trials across sex. Sprague-Dawley rats (25 males, 23 females) were surgically prepared with electrophysiological recording electrodes in the IL and NAcSh as well as tACS headgear, and a cannula for intraoral (IO) infusions. Rats received 30 IO infusions of saccharin (0.15%, 3.5 s infusions on a variable-time 30 s schedule) followed by lithium chloride (LiCl; 127 mg/kg, i.p.) to induce CTA. Two days later, rats underwent tACS (18 µA sine wave @ 80 Hz with 10 s stimulation on and 10 s stimulation off for 13.5 minutes/day) or sham (attached to tACS system but no stimulation delivered) for 7 days. Rats then underwent CTA testing followed by 4 extinction days involving intraoral saccharin delivery only. After the final extinction day, rats received another 7 days of tACS or sham treatment as above, then underwent innate aversion testing where they received 30 IO infusions of quinine. Affective state was assessed using taste reactivity methods; LFPs were simultaneously recorded from IL-NAcSh in a subset of male (n = 17) and female (n = 15) rats. We found that male rats given tACS exhibited an enhanced CTA compared to shams, while females demonstrated decreased CTA behavior compared to shams. Further, tACS altered innate aversion in male but not female rats, compared to shams. These results indicate a clear sex difference in the effects of high gamma 80 Hz tACS on learned and innate aversion. Ongoing studies are examining the effects of 80 Hz tACS on IL-NAcSh LFP activity to explore how tACS may alter signaling within this system and its association with behavioral changes.

Disclosures: E. Grablin: None. **R.M. Carelli:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.02/DD23

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIMH F32MH133387
NIH T32 NS115753
NIMH R01MH127214
NIH K01MH116264

Title: Directed cell-type recruitment during consolidation of a remote memory

Authors: *Z. ZEIDLER[1], A. YU[3], L. A. DENARDO[2];
[2]Physiol., [1]UCLA, Los Angeles, CA; [3]Psychiatry, Yale Univ., New Haven, CT

Abstract: Memories are consolidated into a distributed neocortical network for long-term storage. Long-term memory retrieval relies on cells that are active during learning and undergo necessary plasticity. However, remote memory retrieval activates a broader circuit, with learning-activated cells representing only a small subset. What are the rules and cell-types governing memory trace reorganization? We identified a class of prefrontal projection neurons that are gradually recruited to a memory trace through synaptic activity of learning-activated cells. This population, which projects to the temporal association area (TEa), progressively strengthens its encoding of memory-induced behaviors, mirroring increases in TEa activity. These neurons project widely across the brain and yet strongly target the claustrum (CLA) during recall. Both TEa and CLA show time-dependent changes to memory encoding yet inhibition of their prefrontal inputs has divergent effects on memory induced behavior at remote but not recent memory retrieval. Our findings reveal a cell type-specific mechanism underlying multi-region memory trace reorganization during consolidation.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.03/DD24

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH R01MH123260-01

Title: Fear Conditioning Preserves Cortical Representations of Sound Duration Through Amygdala-Auditory Cortex Circuits

Authors: *P. M. OGALLAR, M. E. NORMANDIN, N. B. COOK, J. T. HUTSON, I. A. MUZZIO;
Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Fear memories enable organisms to detect and respond to potential threats, yet the neural mechanisms that support the long-term storage and flexible updating of auditory fear associations remain poorly understood. Although the primary auditory cortex (A1) undergoes substantial plasticity following fear conditioning, its contribution to remote memory retrieval and extinction learning remains controversial. Here, we combined longitudinal calcium imaging and optogenetic manipulation of lateral amygdala (LA) projections to A1 to examine how auditory cortical representations evolve during recent and remote fear memory retrieval. Mice were trained in an auditory fear-conditioning task in which white noise was paired with foot shock and were tested at recent and remote time points. Longitudinal calcium imaging revealed that fear conditioning produced persistent changes in auditory cortical population activity. Whereas control animals exhibited a progressive attenuation of sound-evoked responses over time, conditioned animals maintained robust responses for at least 30 days after learning. Optogenetic inhibition of excitatory LA→A1 projections disrupted the maintenance of these long-term population representations, suggesting that amygdala inputs contribute to the stabilization of remote auditory fear memories. Classification of individual neuronal response profiles revealed multiple sound-responsive cell types whose distribution changed over time. Conditioned animals displayed an increased representation of onset-responsive neurons following conditioning, as well as enhanced sustained responses during remote retrieval, whereas control animals showed a greater proportion of delayed-onset responders. Inhibition of LA→A1 projections selectively reduced the prevalence of sustained-responsive neurons, suggesting that amygdala inputs are required for maintaining cortical representations of stimulus duration. Moreover, population activity patterns were more consistent across repeated sound presentations in conditioned animals, whereas consistency decreased in control mice and following LA→A1 inhibition. Together, these findings demonstrate that A1 maintains long-term temporal representations of behaviorally relevant sounds and that LA inputs are essential for stabilizing these representations over time. These circuit interactions may contribute to the enhanced salience of threat-predictive auditory stimuli following fear learning.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.04/DD25

Topic: H.01. Fear and Aversive Learning and Memory

Title: VTA Dopamine Neurons Drive Learning through Valence Prediction Error

Authors: *E. J. MAES[1], A. USYPCHUK[2], M. D. IORDANOVA[3], G. SCHOENBAUM[5], A.-L. SCHLENNER[4], M. P. GARDNER[6], D. K. AVRAMIDIS[7];
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Pierrefonds, QC, Canada; [5]NIDA IRP, BALTIMORE, MD; [6]Cell. Neurobio. Res. Br., NIDA IRP, Montreal, QC, Canada; [7]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The phasic firing of ventral tegmental area (VTA) dopamine (DA) neurons is generally recognised as signalling prediction error to support learning about reward. Evidence for a role of dopamine as a general prediction error signal has primarily been via learning about sensory events. However, evidence for the role of DA in learning about aversive events remains mixed. In fact, there is support that this signal drives learning across reward and aversion through a common "valence-free" error, an increase in firing to appetitive and aversive events, as well as a signed "valence-based" error, where appetitive and aversive events have opposing effects on VTA DA firing. Reconciling these observations is difficult. We addressed these questions using behavioral electrophysiology and optogenetics. First, we recorded single-unit activity of VTA DA neurons in freely-moving rats performing a Pavlovian task, where auditory cues were paired with either aversive footshock or sucrose reward. Using a theory-informed decoder approach, we found that DA neurons form two distinct populations coding for trial identity and valence prediction error, where *Valence-PE* neurons represented outcome omission as state of opposite valence (e.g. shock omission as reward expectancy). Furthermore, Valence-PE neurons exhibited phasic excitation and inhibition in response to reward- and shock-predicting cues, respectively. Optogenetic inhibition that mimicked the decrease in DA neuron activity during shock-predicting cues enhanced cue-reinforced aversive (second-order) conditioning, whereas optogenetic excitation impaired it. We also found that optogenetic excitation of VTA DA neurons attenuated aversive prediction error and enhanced blocking, an effect opposite to that typically observed in the reward-learning domain. These studies provide causal evidence that DA neurons promote aversive learning through suppression, and that increases in DA activity oppose aversion to both predictive cues and aversive outcomes. Together these data afford crucial support to the proposal that individual VTA DA neurons drive learning across reward and aversion through signaling valence-based prediction error.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.05/DD26

Topic: H.01. Fear and Aversive Learning and Memory

Support: Intramural Research Program of NIH

Title: iMOSS: An integrated open-source tail suspension test platform for high-resolution immobility scoring and synchronization with neural activity

Authors: *Z. YE[1], X. MIN[1], S. JOHNSON[1], X. CAO[2], S. IKEMOTO[1];
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Abstract: The tail suspension test (TST) is widely used to assess stress-coping behavior in rodents, characterized by alternating periods of active (struggling) and passive (immobile) responses. Immobility in the TST is interpreted as behavioral despair and serves as a key measure for screening antidepressant compounds. However, traditional manual scoring relies on continuous video playback, making it labor-intensive and temporally imprecise due to human reaction lag. Conversely, existing automated systems are prone to behavioral misclassification or lack integration with modern neural recording modalities. To address these limitations, we developed iMOSS (Immobility/Mobility Optimized Scoring System), an open-source, low-cost, and scalable platform comprising two complementary, high-resolution tools: (1) iMOSS-MV, a video-based frame-by-frame manual scoring software that eliminates real-time observation lag, serving as both an highly efficient standalone annotation tool and a superior, frame-accurate gold standard for validation, and (2) iMOSS-AS, a sensor-based automated instrument that detects immobility/mobility bouts using a machine learning-optimized threshold. We validate that iMOSS-AS output closely matches the precise iMOSS-MV benchmark and outperforms existing alternatives. Additionally, both tools reliably detected changes in behavioral dynamics induced by antidepressant imipramine, confirming sensitivity to pharmacological manipulations. Finally, we demonstrate the platform's utility for systems neuroscience by seamlessly integrating iMOSS behavioral metrics with simultaneous fiber photometry recordings of medial septal glutamatergic calcium activity. Together, the iMOSS platform provides an efficient, user-friendly, and bias-minimized solution for high-throughput behavioral profiling, enabling seamless alignment of physical movement with high-resolution neural dynamics.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

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Program #/Poster #: PSTR105.06/DD27

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIAAA Intramural Research Program

Title: Regulation of Fear Memory Formation by Intercalated Amygdala Neurons

Authors: *S. VARADA, O. BUKALO, N. RAY, N. DERMADY, H. BHAGWAT, S. MOSLEY, O. CARPENTER, S. ZIMMERMAN, V. OFFENBERG, A. HOLMES;
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Abstract: The ability to form associations between environmental cues and threatening experiences is essential for survival and depends on neural circuits that support fear learning. Within the amygdala, intercalated cell (ITC) clusters comprise specialized GABAergic neuron

populations that surround the basolateral amygdala (BLA) and play important roles in regulating fear-related behaviors. Here, we examined the contribution of the dorsomedial ITC (ITC_{dm}) cluster to the formation of fear memories. Using FoxP2-Cre transgenic mice, we selectively targeted ITC_{dm} neurons and performed bulk-calcium fiber photometry in freely behaving animals undergoing fear conditioning and extinction. Results revealed strong activation of ITC_{dm} neurons to aversive footshocks. To determine the functional significance of this activity, we chemogenetically manipulated ITC_{dm} neurons during fear conditioning. Chemogenetic inhibition of ITC_{dm} neurons activity enhanced subsequent fear retrieval and caused fear generalization, supporting a role for ITC_{dm} neurons in regulating fear memory formation and discrimination. Fiber photometry demonstrated that ITC_{dm} inhibition increased stimulus-related activity in lateral amygdala (LA) neurons during fear conditioning, suggesting that ITC_{dm} neurons constrain LA-encoding of weak or ambiguous aversive information. By contrast, projection-specific inhibition of ITC_{dm} outputs to basal amygdala (BA) or ventromedial ITC (ITC_{vm}) revealed distinct circuit-dependent effects on fear expression and memory retrieval. Ongoing studies investigate how convergent sensory inputs from thalamic and cortical pathways influence ITC_{dm} neurons function during fear learning. Collectively, these findings identify ITC_{dm} as a key regulatory node within amygdala networks that controls fear learning through both input and output-specific mechanisms.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.07/DD28

Topic: H.01. Fear and Aversive Learning and Memory

Support: Penn State College of Medicine
PA Department of Health

Title: Dynamic Beta2-Adrenergic Receptor Signaling in vBNST CRF Neurons Gates Stress-Induced Avoidance Memory

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Abstract: Avoidance is a core feature of stress-related disorders, yet the molecular mechanisms underlying persistence of avoidance behaviors remain unclear. Prior work from our group identified a critical role for beta2-adrenergic receptor (Adrb2) signaling in ventral bed nucleus of

the stria terminalis (vBNST) corticotropin-releasing factor (CRF) neurons in consolidating stress-avoidance memory in mouse models. Here, we tested how Adrb2 dynamics regulate the formation and persistence of stress avoidance. Adult male mice (n=5-10/group) were exposed to predator odor and restraint stress and assessed for avoidance at 24 h and 28 days. Combined stress produced robust long-term avoidance, which was reduced by Adrb2 antagonism and global CRF-Adrb2 knockdown. Viral approaches were used to selectively overexpress or knockdown Adrb2 in BNST CRF neurons, and spatial transcriptomic analyses were performed using RNAscope and STARmap. Despite confirmed virally-mediated increases or decreases in Adrb2/CRF mRNA colocalization, overexpression failed to enhance stress-avoidance and knockdown failed to reduce avoidance. Acute stress induced transient upregulation of Adrb2 in CRF neurons, but no sustained expression changes were observed. Glucocorticoid receptor signaling contributed to stress-induced Adrb2 upregulation, and downstream signaling pathways remained altered independent of sustained receptor expression. Together, these findings reveal that static manipulation of Adrb2 is insufficient to drive avoidance and instead support a model in which temporally restricted, stress-evoked Adrb2 signaling acts as a coincidence detector to trigger downstream plasticity long-term. We propose that transient Adrb2 activation during stress is required for encoding avoidance memory, whereas long-term maintenance is mediated by downstream network adaptations. This mechanism refines understanding of BNST CRF-noradrenergic interactions and identifies temporally gated Adrb2 signaling as a key process underlying stress memory formation.

Disclosures: Y. Silberman: None. **J. Snyder:** None. **A. Hajnal:** None. **J.D. Gross:** None. **J.E. Ploski:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.08/DD29

Topic: H.01. Fear and Aversive Learning and Memory

Support: CIHR Project Grant
Brain and Behaviour Research Foundation (NARSAD New Investigator Award)
Canada Research Chair Tier 2
Concordia University Tuition Remission Award
Nadia Chaudhri Wingspan Award

Title: Orbitofrontal-amygdala circuits link fear with the past and the future

Authors: *D. E. GOSTOLUPCE[1], B. LAY[5], T. SLOAN[6], M. J. WILLIAMS-SPOONER[2], B. MISIC[7], G. ESBER[3], M. D. IORDANOVA[4];
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Abstract: A traumatic experience not only conditions fear to cues present during the event itself but can also generalize fear backward and forward in time to cues that were never encountered during the trauma. Assigning fear with different gradients across the memory network can be adaptive, however, this process of multiplying triggers for fear can also undermine the effectiveness of interventions designed to reduce maladaptive fear. Understanding how the brain supports the spread of fear across time is critical to understanding the architecture of flexible memories and how those memories control maladaptive behaviour. Here we used two well-established associative learning designs which mimic the spread of fear to cues experienced *before* (retrospective) or *after* (prospective) a primary fear conditioning event. We show that the spread of fear backward (retrospectively) and forward (prospectively) in time is dissociable at the behavioural and neural level, relying differentially on retrieval of the primary fear memory, and activating unique ensembles of neurons in the basolateral amygdala and the lateral orbitofrontal cortex. Functional circuit interrogation revealed that while linking fear retrospectively to past experiences relies on a feedback loop between the BLA and OFC, linking fear prospectively to stimuli experienced after the primary fear conditioning event depends on BLA input to the OFC but not the reverse. Lastly, we identified the brain-wide network connectivity of the BLA and OFC during retrospective and prospective fear linking, revealing that the retrospective fear network exhibits a more integrated architecture that maintains the tight coupling of memories across time. Moreover, the BLA and OFC form distinct functional communities in both networks, however, in the retrospective configuration these regions are positioned to coordinate activity across other influential nodes, whereas their regulatory influence appears more limited within the prospective network. Together these findings uncover a key dissociation in the neural basis of how fear spreads across time linking with events experienced before and after a fear conditioning episode and reveal a novel player, the lateral OFC, that ought to be integrated into a wider, flexible fear network.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.09/DD30

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01MH132223

Title: Inhibition of basolateral amygdala projections to the medial entorhinal cortex impairs the consolidation of inhibitory avoidance and contextual pre-exposure.

Authors: *A. R. HOLM[1], R. T. LALUMIERE[2], J. J. RADLEY[3];
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Abstract: Considerable evidence indicates that the basolateral amygdala (BLA) modulates the consolidation of many different types of learning. Previous work from our laboratory found that projections from the BLA to the medial entorhinal cortex (mEC) influence the consolidation of spatial/contextual memories in a spatial Barnes maze task, though the role of this pathway in the consolidation of inhibitory avoidance (IA) learning, a task that also involves contextual learning, is unknown. A separate study from our laboratory found that pre-exposure to the training ("aversive") context in IA promoted memory strength (i.e., degree of retention in the training chamber) and increased precision (i.e., degree of discrimination vs. generalization to other similar contexts) at both a recent retention test and a remote retention test, compared to training without a contextual pre-exposure. Based on these prior findings, the present work examined the BLA-mEC pathway in IA memory consolidation and in the consolidation of aversive context pre-exposure. As memories shift in their strength and precision over time, the present studies tested retention at both recent and remote timepoints after training to determine whether altering activity in this pathway during consolidation had differential effects depending on the time of retrieval. In the first experiment, male and female Long-Evans rats received intra-BLA viral injections containing the inhibitory opsin eNpHR3.0 (or a control eYFP vector) and optical fiber implants aimed at the mEC. Rats then underwent training on a single-trial step-through IA task, followed by 15 min of optogenetic inhibition of the BLA-mEC pathway. Retention tests occurred in both the aversive and neutral contexts at recent and remote timepoints. Results indicate that rats that received BLA-mEC inhibition immediately after training had impaired memory strength at recent and remote timepoints. In a separate experiment, rats were given a 5-min pre-exposure to the aversive context, followed by 15 min of BLA-mEC inhibition. One day later, the rats underwent IA training, with retention tests in the aversive and neutral context at recent and remote timepoints. Preliminary results reveal that rats that received BLA-mEC inhibition immediately after pre-exposure had reduced memory precision at both timepoints. Together, these findings provide insight into the function of the BLA-mEC pathway in IA memory consolidation.

Disclosures: A.R. Holm: None. **R.T. LaLumiere:** None. **J.J. Radley:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.10/EE1

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH R00MH121563

Title: Valence and behavior encoding in the dorsal striatum during fear learning

Authors: *K. J. LEE[1], N. POLL[2], F. BUSHRA[3], D. LEMMON[6], A. DILIBERTO[2], C. R. HEYMAN[4], M. MAUGHAN[5], F. MILLS[1];
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Abstract: Although the dorsal striatum (DS) has been extensively studied in reward-guided learning and action selection, comparatively little is known about its role in fear learning. D2-expressing medium spiny neurons (D2+ MSNs) have been implicated in aversive processing and behavioral suppression, yet how they encode threat-predicting cues during fear conditioning remains unclear. Here, we examined neural representations of cue valence and behavior in D2+ MSNs during a multi-stage associative learning task in which mice learned to discriminate reward-, punishment-, and neutral-predicting cues. Using *in vivo* calcium imaging (GCaMP8m) in freely moving mice (n = 23; 11 male, 12 female; 1385 D2+ neurons), we found that distinct subpopulations of D2+ MSNs preferentially encoded cues associated with different outcomes. Following Pavlovian fear conditioning, approximately 33.5% of recorded neurons developed conditioned responses to the punishment-predicting cue. These responses were significantly different from responses to reward-predicting and neutral cues, consistent with valence-selective rather than salience-driven encoding (one-way ANOVA, $F(2,327) = 143.4$, $p < 0.0001$). To dissociate neural activity related to defensive behavior from cue valence, we quantified subsecond defensive behavioral motifs during recording sessions. This analysis identified separable populations of D2+ MSNs associated with cue valence and defensive actions, respectively. Together, these findings provide a single-cell resolution characterization of dorsal striatal activity during fear learning and reveal distinct D2+ MSN populations that encode threat-predictive information and defensive actions, expanding current models of striatal function beyond reward-guided behavior.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.11/EE2

Topic: H.01. Fear and Aversive Learning and Memory

Title: Short-term enriched environment exposure disrupts fear memory reconsolidation through the medial entorhinal cortex-dentate gyrus circuit

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Abstract: Persistent fear memories can recover after extinction and contribute to trauma-related psychiatric disorders. Memory retrieval renders a consolidated memory transiently labile, creating a reconsolidation window for updating maladaptive fear. Here, we asked whether short-term enriched environment (EE) exposure after retrieval can disrupt fear memory reconsolidation in rats and identified the underlying circuit mechanism. Adult rats were trained in a conditioned fear memory paradigm. After memory retrieval, rats were exposed to short-term EE or standard housing, followed by tests for fear expression, spontaneous recovery, and reinstatement. To define the mechanism, we combined chemogenetic manipulations, activity-dependent engram cell labeling, viral tracing, immunofluorescence, and single-cell RNA sequencing. Post-retrieval EE markedly decreased subsequent freezing and reduced spontaneous recovery and reinstatement, indicating interference with reconsolidation rather than transient suppression of fear expression. Chemogenetic inhibition of dentate gyrus (DG) neurons before EE abolished the fear-reducing effect, demonstrating that DG activity is required. EE also decreased the number of reactivated DG fear engram cells, and selective chemogenetic regulation of these engram cells mimicked or reversed the behavioral effect of EE. Circuit analyses showed that the medial entorhinal cortex (MEC) and its projection to the DG are critical for this process: inhibition of MEC neurons or MEC-DG projections disrupted EE-induced attenuation of fear memory. Single-cell transcriptomic analyses further revealed that post-retrieval EE induced transcriptional changes in DG cell populations, including alterations in genes related to memory-associated plasticity. Together, these results demonstrate that short-term post-retrieval EE disrupts fear memory reconsolidation through MEC-DG circuit engagement and remodeling of DG engram reactivation. These findings support EE as a mild, non-aversive, non-pharmacological strategy for targeting maladaptive fear memories and provide circuit-level insight into behavioral interventions for trauma-related disorders.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.12/EE3

Topic: H.01. Fear and Aversive Learning and Memory

Support: IZLCZ0_206045
IZLIZ3_200297
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3200-0-239999
Synapsis Foundation No. 2020-PI02

Title: Oxytocin Signalling in the mPFC-BLA Circuit Supports Socially Buffered Fear Memory

Authors: *S. CHEN[1], D. CASEIRO[1], R. TOMÀ[1], R. NIU[2], Y. TANG[2], E. VAN DEN BURG[2], C. T. LI[3], R. STOOP[1];

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Abstract: Previously, we found that social buffering of fear (SBF) shifts conditioned-stimulus-evoked activity in the central amygdala from fear-encoding neurons to a distinct population of oxytocin-sensitive buffer neurons, consistent with a switch from fear to safety encoding in this region (Hegoburu C et al., Nat Commun. 2024). Although this was associated with a persistent reduction in fear expression, the underlying circuit and cellular mechanisms remain poorly understood. Here, we investigated whether OT signalling within the medial prefrontal cortex (mPFC)-basolateral amygdala (BLA) circuit contributes to the long-term fear attenuation following SBF.Pharmacological blockade of OTR signalling in the prelimbic cortex (PL), but not the infralimbic cortex (IL), disrupted the formation of long-term SBF memory (N = 16 rats). In addition, chemogenetic silencing of mPFC OTR-expressing neurons impaired SBF memory without affecting initial SBF acquisition (N = 10), suggesting that these neurons are required for maintaining social safety memories.Neural tracing revealed a topographically organized mPFC-BLA projection. BLA-projecting mPFC neurons originated predominantly from ipsilateral layer 2/3 and contralateral layer 5/6, with sparser projections from ipsilateral layer 5/6 and contralateral layer 2/3 (N = 7). Using OTR-Cre rats, we found that OTR-expressing mPFC neurons were predominantly GABAergic neurons (81.1%; N = 2, n = 281 cells).To determine whether fear conditioning and SBF are associated with persistent changes in downstream BLA neuronal function, we performed whole-cell slice recordings from BLA neurons located among fluorescent mPFC-derived fibers while optogenetically stimulating mPFC-to-BLA projections. All recorded neurons (n = 54 from N = 4 control, N = 5 fear recall, and N = 4 SBF memory rats) were responsive to mPFC fiber stimulation. Compared with neurons from fear recall rats, neurons from SBF memory rats showed reduced spontaneous firing rates (from 1.65 to 0.40 Hz, n = 24 and 14 cells, $p = 0.0023$). These changes were accompanied by alterations in action potential half-width (from 1.39 to 1.21 ms, $p = 0.0070$) and maximal repolarization rate (from 153.14 to 181.73 mV/ms, $p = 0.0196$), suggesting persistent modifications in the intrinsic excitability of BLA neurons receiving mPFC input.Together, these results suggest that SBF engages OTR-expressing inhibitory mPFC neurons, particularly within the PL, to support long-term social safety memory and fear attenuation, while inducing lasting plasticity in downstream BLA neurons that may underlie the persistent suppression of fear expression.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.13/EE4

Topic: H.01. Fear and Aversive Learning and Memory

Support: MH117791

Title: Zona incerta firing reflects learned threat probability, not attention, during probabilistic fear discrimination

Authors: *S. SMYTH[1], M. MOADDAB[2], M. A. MCDANNALD[3];
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Abstract: Discriminating between dangerous and safe events is essential for survival. A failure to discriminate, termed fear generalization, results in treating safe stimuli as if they were dangerous. While neural circuits for fear acquisition have been extensively studied, neural circuits for fear discrimination remain unclear. Evidence suggests that the zona incerta, a subthalamic structure, contributes to fear generalization and discrimination. The goal of this study was to examine zona incerta activity while rats undergo a challenging fear discrimination procedure. Adult Long Evans rats (n = 7, 5 females) were implanted unilaterally with drivable microelectrode bundles dorsal to the zona incerta. Following recovery, we recorded zona incerta activity while rats underwent fear discrimination consisting of three 10-s auditory cues, predicting unique foot shock probabilities: danger (p = 1), uncertainty (p = 0.25), and safety (p = 0). Each session consisted of 24 trials: three danger trials, three uncertainty shock trials, nine uncertainty omission trials, and nine safety trials with an average inter-trial interval of 3.5 min. The schedule for rewarded nose poking was completely independent of cue presentation and foot shock. Conditioned suppression ratios were calculated as an indicator of fear discrimination. We recorded 456 neurons over 76 sessions from the zona incerta. Rats showed complete discrimination during sessions in which zona incerta neuron activity was recorded. Zona incerta neuronal firing showed a global pattern of firing inhibition in response to threat cues (danger and uncertainty). Within this global pattern, two functional populations were apparent. One population (n = 192) showed sustained inhibition during the threat cues, while a second population (n = 144) showed an initial inhibition to the threat cues, which was followed by ramping excitation towards cue offset. While sustained zona incerta neuron firing reflected threat probability, dynamic firing first functioned as a general threat detector (danger = uncertainty > safety), before reflecting threat probability. The results reveal the zona incerta as a neural node for detecting and representing environmental threats.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.14/EE5

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIAAA Intramural Research Program

Title: Basolateral amygdala astrocytes shape fear and extinction learning

Authors: *O. BUKALO[1], R. O'SULLIVAN[1], Y. TANISUMI[2], J. O'MALLEY[3], S. VARADA[1], N. RAY[1], N. DERMADY[1], A. MENDEZ[1], S. ZIMMERMAN[1], V. OFFENBERG[1], O. CARPENTER[1], H. BHAGWAT[1], S. MOSLEY[1], J. GOLDSCHLAGER[1], M. A. PENZO[3], L. R. HALLADAY[4], H. WAKE[2], A. HOLMES[1];
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Abstract: Adaptive responses to threat rely on associative learning mechanisms that promote defensive behaviors, as well as extinction processes associated with reduced fear when danger is absent. Disruption of these processes contributes to trauma- and stress-related disorders. The basolateral amygdala (BLA) is a critical node in the neural circuitry underlying fear and extinction memory, where interactions among distinct cellular populations shape behavioral responses. While previous studies have largely focused on neuronal mechanisms, growing evidence suggests that astrocytes play an active role in regulating information processing within amygdala circuits. Using *in vivo* fiber photometry and two-photon calcium imaging, we previously demonstrated that BLA astrocyte activity dynamically tracks changes in fear state and supports neural representations underlying fear memory. Chemogenetic manipulation of BLA astrocytes revealed bidirectional regulation of fear retrieval. In complementary experiments, modulation of astrocytic calcium signaling enhanced the encoding of fear-related cues by neuronal populations within a prelimbic cortex-amygdala circuit. Building on these findings, we investigated the contribution of BLA astrocytes to extinction learning. Using temporally controlled manipulations of astrocytic signaling during extinction, we examined how astrocyte activity influences the acquisition and expression of extinction memory. Our results indicate that astrocytes are critical for extinction memory formation. Ongoing studies seek to characterize neuronal dynamics associated with these effects and define the circuit mechanisms through which astrocytes influence extinction. Together, these findings support a model in which astrocytes are integral components of amygdala circuits that regulate both fear and extinction memories. By extending beyond traditional neuron-centric frameworks, this work highlights astrocytes as active participants in adaptive emotional learning and potential targets for therapeutic intervention in trauma-related disorders.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.15/EE6

Topic: H.01. Fear and Aversive Learning and Memory

Support: DA052108
DA061974

Title: Sex-Specific Reorganization of Frontostriatal and Large-Scale Network Dynamics during Aversive Memory Extinction

Authors: *J. E. DOUTON[1], R. M. CARELLI[2];
[2]Psychology and Neurosci., [1]The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The ability to flexibly adapt behavior to environmental change is critical for regulating aversive memories, as persistent responses can contribute to the emergence of negative affective states, which are implicated in many psychiatric disorders. Prelimbic (PrL)-nucleus accumbens core (NAcC) and infralimbic (IL)-nucleus accumbens shell (NAcSh) pathways are thought to differentially support salience, motivation, and affective valuation, and we have previously shown how they encode the emergence of negative affect in males and female rats. However, how these circuits reorganize their activity to guide behavioral adaptations during negative affect extinction remains poorly understood, particularly across sex. Here, we extended prior findings by using conditioned taste aversion (CTA) induced by lithium chloride (LiCl; 127 mg/kg, i.p.) and assessed its extinction across four days using intraoral saccharin delivery (0.15%, 3.5 s infusions on a variable-time 30 s schedule). Affective state was assessed using taste reactivity, while local field potentials (LFPs) were simultaneously recorded from IL-NAcSh and PrL-NAcC circuits in male (n = 17) and female (n = 15) Sprague-Dawley rats during CTA acquisition and extinction. We found sex- and circuit-specific changes in oscillatory dynamics and connectivity. In males, CTA increased IL resting-state activity, and IL-NAcSh oscillatory activity and synchrony elicited by saccharin dynamically tracked behavioral extinction. In females, IL resting state activity and saccharin-evoked oscillatory power exclusively decreased during early extinction, accompanied by the emergence of IL-NAcSh desynchronization. The PrL-NAcC circuit showed minimal changes in males but exhibited a dynamic oscillatory reorganization during CTA extinction in females but without corresponding synchrony changes. Principal component analysis of LFP features followed by linear mixed-effects modeling revealed a hierarchical sequence in males from baseline to a task-related affective/neural state and subsequent neural reconfiguration, whereas in females, affective state was better explained by a parallel contribution of these neural features. To complement CTA findings, resting state fMRI before and after CTA acquisition revealed that, although some changes in salience network and default mode network connectivity were shared across sexes, CTA primarily produced sex-specific changes in large-scale functional connectivity. Overall, these results show that CTA and its extinction are governed by sex-specific frontostriatal reorganization that differs in how neural dynamics translate into affective state.

Disclosures: J.E. Douton: None. **R.M. Carelli:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

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Program #/Poster #: PSTR105.16/EE7

Topic: H.01. Fear and Aversive Learning and Memory

Support: NHMRC Ideas grant (APP2002877)
University of Sydney Postgraduate Award (UPA)

Title: Chronic neuropathic pain alters fear learning and associated amygdala circuitry

Authors: *K. E. ANDERSON[1], B. L. WINTERS[1], C. W. VAUGHAN[2];
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Abstract: Chronic neuropathic pain is a highly prevalent, disabling, and costly pain syndrome which is associated with debilitating psychological co-morbidities related to abnormal fear learning. The lateral amygdala has been shown to play a key role in integrating the sensory components of fear memory and both the acquisition and expression of conditioned fear. However, little is known about how fear learning and its associated brain regions are affected by animal neuropathic pain models.
In this exploratory study, adult male C57BL/6 mice (n = 8 per group) underwent either chronic constriction injury (CCI) or control sham surgery; sex differences were not assessed. Mice were then subjected to a Pavlovian fear conditioning protocol, and the extent of fear-induced freezing behaviour was quantified to determine changes in fear learning and extinction. A separate cohort of CCI and sham mice was used in brain slice electrophysiology experiments to examine synaptic transmission onto lateral amygdala neurons (n = 8 per group).
It was found that, following fear conditioning, CCI mice displayed altered expression of fear learning and a reduced ability to extinguish cue-driven fear responses compared to sham mice. Electrophysiology experiments showed that, unlike sham mice, evoked AMPAR-mediated excitatory postsynaptic currents (EPSCs) in CCI mice displayed inward rectification, indicating the expression of calcium-permeable, GluR2-lacking receptors. In addition, evoked EPSCs in CCI mice showed a reduced AMPA paired-pulse ratio, indicating altered presynaptic excitability, along with changes in the AMPA:NMDA receptor expression ratio.
These findings suggest that chronic neuropathic pain disrupts fear memory and is associated with pre- and postsynaptic modifications in the lateral amygdala, a crucial substrate for this learning process.

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Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

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Program #/Poster #: PSTR105.17/EE8

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant R01MH131808

Title: Differential innervation of principal neurons in anterior and posterior basolateral amygdala by parvalbumin and cholecystokinin inhibitory interneurons.

Authors: M. E. WILBER, J. D. HUGHES, J. W. WARREN, *D. D. MOTT;
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Abstract: Somatic inhibition in the basolateral amygdala (BLA) plays a critical role in determining whether and how BLA pyramidal neurons/principal neurons (PNs) fire. We immunolabeled BLA tissue from two adult male C57BL/6J mice for glutamic acid decarboxylase 65/67 (GAD65/67) to label GABAergic terminals as well as for parvalbumin (PV) and CB1R to label PV and cholecystokinin (CCK) terminals, respectively. In agreement with prior work, we found that 93% of GAD-positive somatic synapses were also positive for PV or CB1R, indicating that the majority of somatic inhibition onto BLA PNs is provided by either PV or CCK interneurons (INs). Because PV and CCK INs operate within distinct networks, exert different forms of inhibitory control over PNs, receive different types of input, and play different roles in behavior, it is important to study the differential regulation of BLA PNs by these interneuron populations. Toward this goal, we examined the distribution of PV and CCK somata and somatic synapses throughout the BLA. We immunolabeled for GluR2/3 to identify PN somata in anterior BLA (aBLA) and posterior BLA (pBLA) tissue from adult C57BL/6J mice (N = 6; 3 male, 3 female). PV terminals and cell bodies were labeled with a PV antibody, and CCK terminals were labeled using a CB1R antibody. We found a greater average density of PV somata in the pBLA compared with the aBLA ($p = 0.001$). Ongoing studies are investigating the distribution of CCK IN somata in the BLA. When examining inhibitory synapses onto PN somata, we found that the average density of CCK synapses was similar between the aBLA and pBLA ($p = 0.234$), whereas average PV synaptic density was significantly higher in the pBLA than in the aBLA ($p = 0.004$), consistent with the greater number of PV somata in this region. When expressed as a PV/CCK synapse ratio, PNs in the aBLA received, on average, similar numbers of PV and CCK synapses. In contrast, PNs in the pBLA received significantly greater innervation from PV than from CCK INs ($p = 0.002$). However, innervation of individual PNs varied substantially, and this variability differed significantly between the aBLA and pBLA, with greater variability observed in the pBLA. Preliminary analyses revealed no sex-dependent differences in PV or CCK synapse distribution. These findings have important implications for inhibitory control of BLA PNs and suggest differential regulation by PV and CCK inhibitory networks in the aBLA and pBLA, consistent with reported differences in the behavioral roles of these brain regions. Ongoing experiments are investigating the impact of these anatomical differences on associative fear learning behaviors.

Disclosures: M.E. Wilber: None. **J.D. Hughes:** None. **J.W. Warren:** None. **D.D. Mott:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.18/EE9

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH R21 MH134183
NIH K99 EY037495-01

Title: Height threat as a context-dependent threat assay in mice

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Abstract: Novel animal models investigating the neural processes underlying threat perception and threat avoidance are vital to identifying biological dysfunctions in anxiety-based disorders. Associative learning paradigms have delineated threat-learning circuits but generally do not allow for the study of threat avoidance. Despite its relevance to human behavior, preclinical literature on height threats as an assay for innate fear is limited. Current paradigms of innate threat rely on predatory fears, which are not evolutionarily conserved or translatable to humans. The elevated plus maze and hole-board exploration test are standards for assessing rodent avoidance and exploratory behavior, but the elevated platform uniquely assays these as competing behaviors. Prior work shows that the elevated platform task itself is context-dependent, where maternal motivation, platform opacity, and height of the platform can impact behavior.
The medial prefrontal cortex (mPFC) is activated by spatial proximity to threat and hypothesized to coordinate escape behaviors, while norepinephrine is released in response to threat and arousal. We examined how the elevated platform uses height as a context-dependent threat assay, testing how internal and external contexts can modify rodent behavior and physiology. Mice are placed on a transparent or opaque 20 cm diameter elevated platform. After 5 minutes of acclimation where the edge was covered, the cover was removed and the number of times the mouse looks down over the edge of the platform ("peers") were counted. Mice increased edge exploration and number of peers in the transparent platform condition. We recorded the release of norepinephrine in mPFC using a GRAB-NE sensor and found that mPFC NE release increases as mice approach the edge, peaks as mice peer, and decreases as they retreat from the edge. Optogenetic manipulation of the noradrenergic system and mPFC revealed that while the number of peers did not change, the extent mice stretched from the edge to explore was greatly increased. We are using computational behavioral tracking and key-point motion sequencing to further characterize the behavioral changes we observed while inhibiting the norepinephrine system and mPFC. These data will be presented at the meeting.

Disclosures: R. Lokanadham: None. **S.M. Staszko:** None. **A.P. Kaye:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.19/EE10

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Intramural Research Funds

Title: Circuit Function of CB1R-Expressing GABAergic Interneurons in the Basolateral Amygdala During Fear Extinction

Authors: *O. GUNDUZ CINAR[1], S. PELAYO[1], C. HIERS[1], J. CROW[1], N. WOODSIDE[1], L. ZWEIFEL[2], Y. LI[3], N. HAJOS[4], A. HOLMES[1];
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Abstract: Endocannabinoid signaling in the basolateral amygdala (BLA) is a critical determinant of fear extinction, yet the inhibitory circuit mechanisms through which it acts remain largely unresolved. Although prior studies from our laboratory and others have established that endocannabinoids modulate glutamatergic cortical inputs to the BLA during extinction learning, whether cannabinoid signaling engages local GABAergic interneuron populations to regulate BLA output has remained unclear. Here, we identify a molecularly defined population of CB1R-expressing GABAergic interneurons in the BLA and establish their essential role in extinction-related circuit function. Using RNAscope and immunohistochemistry, we found that gamma-synuclein (Sncg) is selectively enriched in BLA interneurons co-expressing GABAergic markers and CB1R, with minimal overlap with excitatory neuronal populations. This molecular signature enabled an intersectional viral strategy for selective targeting of Sncg+ GABAergic interneurons in the BLA. Optogenetic silencing of these cells during extinction training markedly impaired extinction acquisition, demonstrating that this interneuron population is required for normal extinction learning. Complementing these findings, CRISPR-mediated disruption of CB1R in GABAergic interneurons impaired extinction memory retrieval, revealing that cannabinoid signaling within inhibitory BLA circuits is necessary for adaptive suppression of conditioned fear. To directly interrogate inhibitory circuit output, we employed fiber photometry to monitor GABA release (using iGABASnFR2) along BLA cortical output pathways. These measurements revealed that inhibitory transmission is dynamically engaged during extinction and is sensitive to endocannabinoid-dependent modulation. Together, these findings identify a previously uncharacterized CB1R-expressing interneuron population in the BLA as a key cellular substrate for fear extinction and define an inhibitory circuit mechanism through which endocannabinoid signaling gates adaptive fear suppression.

Disclosures: O. Gunduz Cinar: None. **S. Pelayo:** None. **C. Hiers:** None. **J. Crow:** None. **N. Woodside:** None. **L. Zweifel:** None. **Y. Li:** None. **N. Hajos:** None. **A. Holmes:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.20/EE11

Topic: H.01. Fear and Aversive Learning and Memory

Support: Department of Neurobiology

Title: Modelling Cued-Threat Discrimination and Generalization Using Cued-Threat Conditioning in Mice

Authors: *B. L. ASARE-OWUSU[1,2], I. WILLIAMSON[3,2], B. JUAREZ[3,2];
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Abstract: Posttraumatic stress disorder (PTSD) and generalized anxiety are thought to arise from a dysfunction in the ability to assess and discern threatening and safe stimuli, which induces generalized threat responses. The parabrachial nucleus is a hub for the brain's affective threat system and has been identified to assess and associate aversive information to modulate behavioral responses. Disorders in this system can cause more maladaptive responses, which may underlie responses associated with PTSD and generalized anxiety. By using a classic associative learning task known as cued-threat conditioning, we can measure behavioral responses to stimuli in mice. Our findings revealed a reproducible paradigm in which the male mice presented with a low shock (0.3mA) were able to discriminate between the CS+ and CS- auditory tones, whilst the high shock mice (0.7mA) were unable to discriminate between the tones which gave rise to generalization. Interestingly, female mice showed discrimination at 0.3mA and maintained discriminative threat processing at 0.7mA. Generalization in females occurred only at a higher shock intensity of 0.8mA. We next sought to determine if rates of extinction of threat responses were the same between discriminative and generalized male mice. We saw that after 30 presentations of both CS+ and CS- auditory cues, discriminative mice reduced their freezing behaviors to both cues, yet generalized mice maintained freezing to CS+ cues, indicating development of discriminative behaviors after extinction learning. Given these findings, we aim to further investigate translational changes using qPCR in regions known to regulate these behaviors.

Disclosures: B.L. Asare-Owusu: None. **I. Williamson:** None. **B. Juarez:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.21/EE12

Topic: H.01. Fear and Aversive Learning and Memory

Support: National Natural Science Foundation of China (32271060)
Natural Science Foundation of Beijing Municipality (IS23073)

Title: Emergent representations of emotional valence in visual cortex and superior colliculus

Authors: *R. TANG[1,2], R. WU[1,2], X. TIANYU[3], C. LI[4], Y.-T. LI[1,2];
[1]Chinese Inst. for Brain Research, Beijing, Beijing, China; [2]Peking Union Med. Col., Beijing, China; [3]Capital Med. Univ., Beijing, China; [4]China Agr. Univ., Beijing, China

Abstract: Visual stimuli can acquire distinct emotional valence through associative learning, and the same visual stimulus may become associated with either positive or negative outcomes depending on experience. Although valence signals have been extensively characterized in downstream structures such as the amygdala, how emotional valence representations emerge in early visual circuits remains poorly understood. Here we developed a head-fixed conditioning paradigm in which upward drifting grating stimuli (conditioned stimuli, CS) were paired with either aversive tail shocks or appetitive water rewards (unconditioned stimuli, US) using forward conditioning, while leftward drifting gratings were presented without reinforcement as controls. Most mice acquired these associations within several days under both conditioning paradigms. Using longitudinal two-photon calcium imaging, we tracked neuronal activity in primary visual cortex (V1) and superior colliculus (SC) throughout learning. We found that a substantial fraction of V1 neurons responded to the US, whereas only a small fraction of SC neurons exhibited US-evoked activity. Despite this difference, associative learning induced pronounced changes in visual responses in both regions. SC population responses represent both appetitive and aversive associations specifically for the conditioned directions. In contrast, learning-related changes in V1 extended beyond the conditioned directions to control directions. Population analyses revealed a progressive separation of positive- and negative-valence representations in both V1 and SC, reflected by increasingly divergent neural trajectories. At the single-cell level, distinct subsets of neurons in both regions exhibited valence-dependent modulation of visual responses, indicating the emergence of positive- and negative-valence ensembles during learning. Together, these findings reveal emergent representations of emotional valence in both cortical and subcortical visual circuits, demonstrating that associative learning can reshape neural representations at early stages of visual processing.

Disclosures: R. Tang: None. **R. Wu:** None. **X. Tianyu:** None. **C. Li:** None. **Y. Li:** None.

Poster

PSTR105: Fear Learning, Memory, Extinction, and Behavioral Adaptation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR105.22/EE13

Topic: I.07. Long-Term Memory

Support: NIH Grant R01MH132223

Title: Machine learning approaches reveal complex behaviors in rats indicative of memory retention, generalization, and sex during inhibitory avoidance tests

Authors: *H. LIU[1], J. COCKBURN[2], R. T. LALUMIERE[2];
[1]The Univ. Of Iowa Neurosci. Grad. Program, Iowa City, IA; [2]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Inhibitory avoidance (IA) is a commonly used aversive associative learning procedure for examining episodic-like memories in which rats receive a footshock in one part of a two-compartment apparatus. Traditionally, the latency to cross from the non-shock (bright) to the shock (dark) compartment has been used as the primary index of memory retention during subsequent testing. However, observations of rat behavior in our laboratory suggest that rats display a variety of behaviors that change as a consequence of the initial training. Moreover, when tested in a contextually similar yet distinct apparatus to assess memory generalization, rats may display a suite of behaviors different from those displayed in the original training apparatus. Therefore, in this study, we used machine learning approaches to examine additional behaviors during testing to determine whether other behaviors might produce a more complex picture of memory retention and generalization. Male and female Long-Evans rats underwent IA training and were tested 2 days and 28 days later by being placed in the original non-shock compartment and given free access to the entire apparatus. Their behavior during testing was recorded for 10 min. Additionally, rats were also tested in a neutral chamber to examine memory generalization. All video analysis and behavioral annotation was done by our machine learning pipeline. Our findings indicate several different behaviors that reflect retention, as assessed in the original apparatus: latency to cross; immobility; stretch-attend; locomotion; and duration in dark compartment. We found that some behaviors reliably indicated high levels of memory discrimination whereas others reliably indicated high levels of memory generalization. We then performed Elastic Net regularized logistic regressions with our behavioral data as independent variables and the sex of animals as the dependent variable. We found that the regression model reliably predicted sex at remote but not the recent tests. In addition, when examining the contribution of predictors, we found that immobility and locomotion contributed most to the model. In summary, we identified multiple measures of memory retention beyond latency that reflect both the retention and generalization of memories. Behaviors like immobility and locomotion, but not latency, showed sex differences at the remote timepoint.

Disclosures: H. Liu: None. **J. Cockburn:** None. **R.T. LaLumiere:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.01/EE14

Topic: H.02. Reward and Appetitive Learning and Memory

Support: UVA Presidential Fellowship

Title: Dorsal hippocampus encodes nonspatial reward experiences and drives goal-directed behavior

Authors: *Y. ZHANG[1], A. DICKERSON[1], L. BELL[1], E. H.-A. NIEH[2];
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Abstract: Hippocampal dorsal CA1 region (dCA1) has a well-established role in spatial navigation and reward-associated learning, yet how dCA1 encodes the distinct phases of instrumental conditioning — action, cue, and reward — and how these representations emerge across learning remains unknown. Existing studies use passive conditioning paradigms tied to spatial cues, making it difficult to isolate reward encoding from place coding or distinguish between neural representations of distinct phases of reward experience.Head-fixed male and female GP5.17 transgenic mice (n=11) expressing GCaMP6f in excitatory neurons underwent two-photon calcium imaging through a cranial window over dCA1 while performing a sucrose self-administration task. In instrumental condition, mice could choose to press an active lever to receive a cue and a sucrose reward, or an inactive lever with neither. A Pavlovian control condition delivered cues and rewards passively during inter-trial intervals. Holographic optogenetic stimulation (n=2 mice, 58 stimulations) targeted neurons active prior to lever pressing, with lever pressing rate compared between stimulation and random non-stimulated time windows. With instrumental conditioning, dCA1 neurons developed firing fields aligned to lever press, cue onset, and reward consumption, with a greater proportion of neurons having firing fields centered at the lever press compared to other task phases. Trial-to-trial population activity correlation revealed a block structure within sessions, suggesting that dCA1 population activity is not uniform across a session but instead reflects distinct behavioral states — potentially corresponding to changes in motivational state such as satiation. Under Pavlovian conditions, firing fields shifted toward the cue period, indicating that the representation of lever press encoding in instrumental trials reflects volitional action rather than sensory responses to the cue or reward. Furthermore, holographic optogenetic stimulation of neurons active prior to lever pressing increased lever pressing rate compared to non-stimulated time windows, establishing a causal role for dCA1 activity in reward-directed behavior.These results demonstrate that dCA1 actively encodes distinct phases of reward experience during instrumental conditioning, with representations that are shaped by the volitional nature of the action rather than sensory properties of the reward alone. The causal evidence suggests that dCA1 ensembles drive reward-directed behavior, establishing dCA1 as an active participant in reward learning and goal-directed behavior beyond its classical role in spatial navigation.

Disclosures: Y. Zhang: None. **A. Dickerson:** None. **L. Bell:** None. **E.H. Nieh:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.02/EE15

Topic: H.02. Reward and Appetitive Learning and Memory

Support: SFB1134_B04

Title: A dual-ensemble model of infralimbic cortex function in behavioural flexibility

Authors: *A. ADLAKHA[1], I. SONNTAG[1], W. H. SOMMER[2], T. KUNER[1];
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Abstract: The infralimbic cortex (IL) has been traditionally assigned as either a behavioural "STOP" region or a facilitator for reward-seeking depending on the task. These conflicting findings could be result of old whole region imaging and manipulations, which can miss out crucial information about ensemble assembly. We reconcile these conflicting views via a dual-ensemble model where the IL houses an action-outcome predictor ensemble and a prediction error ensemble that dynamically track predictive accuracy. We performed longitudinal in vivo calcium imaging using head-mounted miniscopes in freely behaving rats across cue-conditioned operant self-administration, extinction, and reinstatement task conditions to isolate different ensembles being recruited across the task. The ensemble dynamics were validated using a predictive coding computational simulation and supervised machine learning classifiers. Rats demonstrated robust action-outcome learning, suppression during extinction, and cue-induced recovery of reward expectation during reinstatement. IL dynamics showed sparse activation embedded within widespread trial-related suppression. Task condition-specific signatures emerged represented by pre-press suppression and post-press activation during self-administration, significant excitation pre-press during extinction, and a combination of the two during reinstatement. Crucially, while individual neurons exhibited cellular instability and high dynamics, the population stabilized, showing a robust reduction in Shannon entropy both within and across self-administration sessions, demonstrating a stable representation of the task within the IL. The simulation model successfully recapitulated these empirical properties through the simulated trials and task conditions. Finally, neural networks trained on the data were able to reliably classify the task conditions, and the timing of the action based on the neuronal activity of the IL. These findings shift the view of the IL from a simple switch region to a dynamic predictive engine. By demonstrating that the IL continuously updates behavioural representations as contingencies change, this hypothesis can act as a new perspective to the field.

Disclosures: A. Adlakha: None. **I. Sonntag:** None. **W.H. Sommer:** None. **T. Kuner:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.03/EE16

Topic: H.02. Reward and Appetitive Learning and Memory

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Penske Endowed Family Chair in Neuromodulation

Title: Prefrontal inhibitory cell types mediate the rapid antidepressant effects of repetitive transcranial magnetic stimulation

Authors: *R. N. AHMED[1], M. W. GONGWER[2], A. QI[1], J. BARRY[1], H. LU[3], M. S. LEVINE[1], C. CEPEDA[1], A. LEUCHTER[1], L. A. DENARDO[2], S. A. WILKE[1];
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Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive form of brain stimulation that elicits neural activity in a target region. Repetitive TMS (rTMS) over the prefrontal cortex (PFC) is effective for the treatment of major depressive disorder (MDD). However, the neural mechanisms underlying its therapeutic effects are poorly understood. To address this gap, our lab developed and validated a system to deliver clinical rTMS protocols in awake mice. Using an accelerated intermittent theta burst stimulation paradigm (aiTBS) we delivered rTMS to dorsomedial PFC (dmPFC) in mice exposed to 2 weeks of chronic corticosterone (CORT), a validated stress protocol. One day of aiTBS reversed behavioral deficits in several depression-related assays, and exerted its therapeutic effects in a cell type-specific manner. This project focused on three classes of inhibitory interneurons in PFC: parvalbumin (PV), somatostatin (SST), and vasoactive intestinal peptide (VIP).
Fiber photometry recordings from each cell type during treatment showed that aiTBS differentially modulates interneuron activity. To characterize the interneuron-specific transcriptional response to aiTBS that may underlie these unique activity profiles, we performed single-nucleus RNA sequencing on dmPFC after aiTBS. We conducted differentially expressed gene (DEG) analysis on these data and found that aiTBS drives DEGs bidirectionally in PV, SST, and VIP neurons. Upregulated DEGs in each interneuron subtype were enriched for synapse-related biological pathways, primarily in SST neurons. We then applied a multicellular factor analysis to identify coordinated transcriptional programs across dmPFC cell types. The variance in gene-by-cell-type pairs was best explained by the latent factor which separated aiTBS and sham (LF1). The top-weighted gene-by-cell-type pairs in LF1 partitioned into aiTBS-biased pairs, which were concentrated in L4/5 IT, PV, and SST neurons. Pathway enrichment of aiTBS-biased pairs implicated synaptic pathways in SST interneurons similar to those enriched in upregulated DEGs.
To test whether aiTBS-induced plasticity mechanisms in SST interneurons are required for its behavioral effects, we chemogenetically suppressed SST activity during aiTBS and studied resulting behavior in two depression-related assays: an approach-avoidance conflict and the forced swim test. We found that suppressing aiTBS-elicited SST activity throughout the treatment day blocked antidepressant-like behavioral outcomes in both assays, suggesting that aiTBS drives inhibitory plasticity in SST-specific prefrontal microcircuits to produce its therapeutic outcomes.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.04/EE17

Topic: H.02. Reward and Appetitive Learning and Memory

Title: A Habenula-Enriched GPCR, GPR151, Regulates Depression-Related Behavior Caused by Inflammation

Authors: L. RIOS[1,2,3,4], Y.-H. LIN[1,2,4], L. YUAN[1,2,4], ***H. ARIAS**[5,1,2,4], L. MOTON[6,1], S. SHABEL[1,2,3,4];
[1]Psychiatry, [2]Neurosci., [3]Neurosci. Grad. Program, [4]Peter O'Donnell Brain Inst., Univ. of Texas Southwestern Med. Sch., Dallas, TX; [5]Psychiatry, UT Southwestern Med. Ctr., Dallas, TX; [6]UT Southwestern Med. Ctr., Spring, TX.

Abstract: Inflammation-associated depression is a clinically important subtype of major depressive disorder in which inflammation is thought to contribute to depressive symptoms. This subtype of depression is often resistant to currently available pharmacotherapies, which act in a regionally non-specific manner across the nervous system and therefore also produce unwanted side effects. Here we test GPR151, an orphan G protein-coupled receptor associated with inflammation and highly expressed in the habenula—a region linked to negative valence and depression—as a potential therapeutic target for inflammation-associated depression. Supporting its therapeutic potential, we find that GPR151 is exceptionally enriched in the habenula and displays conserved topography and similar expression relationships with other habenular markers in mice and humans. Consistent with a role in inflammation-associated depression, male Gpr151 knockout mice had reduced passive coping after lipopolysaccharide (LPS) inflammatory challenge, despite showing similar decreases in body weight and immune activation as littermate controls. Restoring GPR151 expression in the adult habenula increased LPS-induced amotivation in male knockout/Gpr151-cre mice without increasing LPS-induced weight loss and immune activation. Female Gpr151 knockout mice also had reduced passive coping after LPS treatment, supporting a role for GPR151 in inflammation-associated depression in both sexes; however, unlike male mice, restoring GPR151 expression in the habenula in females was insufficient to increase LPS-induced amotivation. Together, these data indicate that GPR151 is a promising therapeutic target for inflammation-associated depression, with potentially different mechanisms of action in males and females.

Disclosures: L. Rios: None. **Y. Lin:** None. **L. Yuan:** None. **H. Arias:** None. **S. Shabel:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.05/EE18

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH T32-DA007234
NIH T32-NS105604
NIH R01 MH129370

Title: Investigating Contributions of the Mediodorsal Thalamus to State Encoding

Authors: *F. P. CURRY[1,2], A. R. WOLFF[3], B. T. SAUNDERS[3];
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Abstract: Through learning, environmental cues signal the identity and value of different sensory states, which is central to guiding decision making. Dysregulation in state encoding can promote aberrant behaviors and is associated with numerous neuropsychiatric conditions, including substance use disorder. While extensive evidence shows that the mediodorsal thalamic nucleus (MD) is highly interconnected with key structures involved in emotional, sensory, and reward processing, whether the MD contributes to state encoding remains unknown. To address this question, we used fiber photometry to record MD calcium signals during a sensory-state guided intermittent-access reward seeking paradigm. Rats were trained to self-administer sucrose paired with an auditory cue on a continuous access schedule. Following training, rats were given intermittent access to sucrose, with availability signaled by a transient sensory context shift - the extinguishing of chamber houselights. This resulted in a binging pattern of sucrose seeking that was tied to state transitions. Rats then completed a "state dissociation" phase by maintaining global state cues established during intermittent access while sucrose was continuously available. Rats were then returned to intermittent access to reestablish state-guided behavior. We found dynamic modulation of the MD across this paradigm. Following the onset of the reward available state in the intermittent access phase, the MD developed a sustained increase in activity. This sustained increase to the state transition diminished in dissociation phase, and reemerged when sucrose availability again relied on the presence of the sensory state signal. Regardless of availability, neuronal activity in the MD exhibited similar patterns to initiation of sucrose self-administration. In additional studies, we conducted fear conditioning, where a different sensory cue signaled a threatening state. In this context, MD neurons also dynamically signaled the sensory state which, together with the sucrose data, suggests that this region is important for integrating information to encode state transitions regardless of valence. Finally, we conducted optogenetic intracranial self-stimulation of the MD, and found that rats do not reliably self-stimulate the MD, suggesting that activation of this region is not inherently reinforcing. These findings suggest the MD may integrate sensory information paired to valenced outcomes to encode global state information, but does not drive reinforcement. Future work will examine how decision making mechanisms in the MD and orbitofrontal cortex are impacted by drug use in models of addiction.

Disclosures: F.P. Curry: None. **A.R. Wolff:** None. **B.T. Saunders:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.06/EE19

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant

Title: Learning-dependent lateral habenula (LHb) dynamic activity during reward seeking in a discrimination task

Authors: *D. DAPHNE[1], A. ZAPATA[2], C. R. LUPICA[3];
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Abstract: Learning-dependent lateral habenula (LHb) dynamic activity during reward seeking in a discrimination task. NIDA-IRP, Cellular and Neurocomputational Systems Branch, Electrophysiology Research Section Deborah Daphne, Agustin Zapata, Carl R. LupicaThe Lateral Habenula (LHb) is a key regulator of reward processing and LHb neuron activation occurs during presentation of aversive stimuli and negative reward prediction errors (RPE). Whereas LHb activation encodes aversive outcomes and reward omission, changes in LHb neuronal activity during learning of stimulus-reward associations remains poorly understood. To address this, we monitored LHb neuron excitability, using fiber photometry, to measure changes in GCaMP8f calcium fluorescence in rats learning of an operant discrimination task. This task included learning that one discriminative stimulus (DS) predicts food reward, and another, a neutral stimulus (NS), predicts no reward availability. Across 6 days of training, rats readily learned the discrimination, as evidenced by increased active-lever presses (aLP) during DS trials and infrequent lever presses during NS trials. Alignment of LHb calcium activity to aLPs during DS presentation revealed a pronounced increase in LHb calcium signal leading up to the aLP, followed by a decrease of calcium signal during reward delivery/consumption. The increased LHb calcium signal associated with the DS became larger as discrimination learning progressed across 6 days, whereas calcium signals during NS presentation remained unchanged. This learning-dependent increase in LHb activity during presentation of a cue predicting reward availability (DS), and not with a cue indicating reward absence (NS), was unexpected because increases in LHb are usually associated with events of negative emotional value. Therefore, our results reveal more complex dynamic changes in LHb activity during reward learning that may be related to anticipation or expectation of reward that could serve to guide risk assessment and motivated behavior.

Disclosures: D. Daphne: None. **A. Zapata:** None. **C.R. Lupica:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.07/EE20

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIAAA Intramural Research Program

Title: Investigating basolateral amygdala interneuron contributions to reward and punishment encoding

Authors: *S. HUSSAIN[1], M. HALFELD[2], M. DEVINE[1], D. L. HAGGERTY[3], P. PIANTADOSI[1], A. HOLMES[4];
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Abstract: The basolateral amygdala (BLA) is a nucleus critical to valence processing, with separable ensembles of pyramidal neurons thought to be responsible for encoding positive valence (i.e., reward) and negative valence (i.e., punishment). How these ensembles are formed remains largely an open question. One potential mechanism through which ensemble formation may occur is through local inhibition, whereby GABAergic interneurons are recruited to dampen the activity of particular ensembles based on local excitation from afferents or BLA pyramidal neuron. Interneurons expressing the calcium-binding protein parvalbumin (PV) are well-positioned to control pyramidal cell excitability in a manner that would allow for valence-specific activity, yet, very little is known regarding their function outside of the realm of negative valence. Here, we used PV-cre mice trained to seek reward in a touchscreen-based operant chamber to examine neural correlates of reward learning, before asking mice to perform a 'risky' decision-making task where operant responses carried a specific probability of being punished. BLA PV interneuron activity was measured using fiber photometry, with data suggesting that their activity was recruited during reward consumption. BLA PV activity spanned the duration of the consumption bout, consistent with a potential role in consumption maintenance. Interestingly, punishment (0.08 mA footshock) also caused strong activation of BLA PV interneurons, with mice shifting their reward preference to a non-punished option across the punishment session. Punishment experience did not alter the encoding of reward consumption, and BLA PV interneuron activity largely did not scale with the intensity of the punishment. These data provide initial evidence for a relationship between BLA PV activity and reward consumption maintenance. Ongoing work seeks to chemogenetically and optogenetically manipulate BLA PV interneuron activity to determine whether persistent PV activity is necessary for reward consumption maintenance. Additionally, to tease apart whether separate groups of PV interneurons respond to valence-specific stimuli (e.g., reward vs. punishment), we will use 1-photon calcium-imaging via head-mounted miniscopes while mice navigate reward/punishment learning.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.08/EE21

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Molecular, Morphological, and Topographic Predictors of Cell-Type-Specific Projection Target among Lateral Habenula Neurons

Authors: *Y.-H. LIN[1,3,4,5], S. BISWAS[3,4,6,5], H. ARIAS[3,4,5], S. SHABEL[3,4,6,5], L. MOTON[2,3,4]; [1]Psychiatry, [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Psychiatry, [4]Neurosci., [5]Peter O'Donnell Brain Inst., [6]Neurosci. Grad. Program, Univ. of Texas Southwestern Med. Sch., Dallas, TX

Abstract: The lateral habenula (LHb) suppresses midbrain dopaminergic signaling through excitatory projections to GABAergic neurons in the rostromedial tegmental nucleus (RMTg) and ventral tegmental area (VTA), but also sends excitatory projections directly to midbrain dopamine neurons. How LHb neurons are organized to selectively target these distinct downstream cell types remains poorly understood. Here, we combined cell-type-specific retrograde tracing, multiplexed fluorescence in situ hybridization, morphology, and spatial mapping to identify molecular, anatomical, and cellular predictors of LHb projection target. We used pseudotyped rabies virus to retrogradely label LHb neurons that project to genetically defined VTA GABA neurons, VTA dopamine neurons, or RMTg GABA neurons. We then performed multiplexed FISH for 12 candidate markers identified from scRNA-seq studies. For each labeled LHb neuron, we quantified marker expression, cell size, and mediolateral, dorsoventral, and anteroposterior position. Preliminary data indicate that LHb neurons targeting VTA GABA, VTA dopamine, and RMTg GABA neurons show partially distinct molecular profiles, suggesting that transcriptional identity contributes to target specificity. However, molecular expression alone only modestly predicted projection target. In contrast, cell size was the strongest single predictor of downstream target identity, indicating that morphology captures a major axis of LHb projection neuron organization. Spatial position also contributed to projection specificity, with the most prominent topographic difference being that RMTg-projecting LHb neurons were located more laterally than neurons projecting to VTA dopamine or VTA GABA neurons. These findings suggest that LHb output pathways are organized by convergent molecular, morphological, and topographic features rather than by a single marker-defined cell class. Because LHb projections to VTA dopamine neurons, VTA GABA neurons, and RMTg GABA neurons likely have distinct effects on midbrain dopamine signaling, this organization may provide an anatomical substrate for generating diverse motivational and aversive signals. More broadly, our results indicate that cell size and spatial location can be powerful predictors of projection-defined LHb neuron identity and should be considered alongside molecular markers when defining habenular cell types and circuits.

Disclosures: Y. Lin: None. **S. Biswas:** None. **H. Arias:** None. **S. Shabel:** None. **L. Moton:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.09/EE22

Topic: H.02. Reward and Appetitive Learning and Memory

Support: PI Startup Fund
CTREE Grant 5T34GM136481

Title: Assessing the Role of NACHO, a Neuronal Nicotinic Acetylcholine Receptor Chaperone Protein, in Cognitive Flexibility

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Abstract: Cognitive flexibility requires successful adaptation to changing environmental conditions and is operationalized through reversal learning, which enables the characterization of operant learning and performance. While cholinergic signaling mediates diverse aspects of cognitive function through nicotinic acetylcholine receptors (nAChRs), including learning and memory, the behavioral consequences of disrupting upstream regulators of nAChRs remain poorly defined. NACHO, a neuronal chaperone protein encoded by the *TMEM35* gene, facilitates the functional expression of multiple major nAChR subtypes and is required for the formation of α7 nAChRs. Given that NACHO$^{-/-}$ mice have previously demonstrated impaired spatial learning and fear memory, and α7$^{-/-}$ mice have exhibited deficits in operant food learning tasks as well as delayed procedural learning, the goal of the present study was to examine whether NACHO removal disrupts operant learning and cognitive flexibility in a reversal learning paradigm. NACHO$^{+/+}$ and NACHO$^{-/-}$ mice were trained to discriminate between two levers to receive a food reward during acquisition, and, upon meeting stable responding criteria, the lever assignment was reversed. The NACHO$^{-/-}$ mice exhibited delayed acquisition of the initial rule, earned fewer pellets, and demonstrated lower rates of active lever pressing across the baseline and reversal sessions. Notably, despite no genotypic differences during the baseline session, NACHO$^{-/-}$ mice had significantly fewer inactive lever presses during the reversal session. Taken together, our results suggest that NACHO-dependent nAChR expression supports rule acquisition, operant task performance, and perseverative responding. As NACHO also influences the expression of nAChRs implicated in mediating the reinforcing properties of nicotine, future studies should examine NACHO$^{-/-}$ mice for nicotine sensitivity via the two-bottle free-choice paradigm.

Disclosures: H. McCamy: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund, California State University San Marcos. **Z. Hassan:** C.

Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund, California State University San Marcos. **K.A. Marquez:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund, California State University San Marcos. **B. Delia:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Grant, Center for Training, Research, and Educational Excellence. **N. Bosley:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **S. Yosick:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund. **Y. Sherafat:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PI Startup Fund, California State University San Marcos.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.10/EE23

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01DA035443

Title: Amygdala-Cortical Circuitry in Cue-Reward Learning

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Abstract: Adaptive decision making relies on the ability to learn associations between environmental cues and rewarding outcomes. These cue-reward associations form the internal model of environmental relationships that enable predictions about what outcomes are available and whether they are currently desirable. Such predictions allow adaptive decision making. Despite their importance, the neural circuit mechanisms by which cue-reward associations are formed remain poorly understood. The basolateral amygdala (BLA) is critical for forming cue-reward associations, and the orbitofrontal cortex (OFC) is required for representing and using expected outcomes to make decisions. The BLA sends distinct projections to lateral (lOFC) and medial OFC (mOFC) subregions, which differentially support decisions based on reward identity and value. This raises a fundamental question: whether BLA conveys similar information that is differentially used by OFC subregions, or transmits distinct, pathway-specific signals to OFC subregions that support different aspects of cue-reward learning? To investigate this, we used projection-specific fiber photometry to record activity in BLA-lOFC and BLA-mOFC pathways during cue-reward Pavlovian learning and separately employed pathway-specific optogenetic inhibition to test their causal contribution to learning. Rewards robustly activate both BLA-lOFC and BLA-mOFC pathways during Pavlovian learning, suggesting that BLA outputs convey outcome-related information to OFC subregions during memory formation. This reward-evoked BLA-lOFC activity is critical for forming the cue-reward associations that allow later guide adaptive decision making. Ongoing work is investigating the function of the BLA-mOFC

pathway. This work provides mechanistic insight into how the brain constructs and updates internal models that guide decision making.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.11/EE24

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH/NIGMS Grant P30GM122733

Title: Opposite neuronal responses to reward cues during extinction in the medial prefrontal cortex and the ventral tegmental area from rats performing a discriminative stimulus reward-seeking task

Authors: B. PAUDEL[1], H. HARRIS[2], Y. CHEN[1], *A. J. DEL ARCO[1];
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Abstract: Behavioral adaptations to changes in reward contingencies are essential for survival. Both the dorsomedial prefrontal cortex (dmPFC) and the ventral tegmental area (VTA) play complementary roles in stimulus discrimination and extinction of reward-seeking behavior. However, how neuronal activity changes in response to contextual cues guide the transition to extinction in both brain areas is not fully understood. We recorded simultaneously and compared neuronal activity patterns in the dmPFC and the VTA during a discriminative stimulus (DS) reward-seeking task before and after changes in reward contingencies (i.e., extinction). Male Long Evans rats (3-4 months) were trained to discriminate between a rewarded (continuous tone; DS+) and non-rewarded (intermittent tone; DS-) cue that ended with the extension of a lever (right or left, counterbalanced). Pressing the DS+ associated lever delivered a sugar pellet. After stable performance, rats (n= 7) were implanted with electrode arrays in the dmPFC (prelimbic area) and the VTA. After surgery, animals were retrained and tested in the DS task for two weeks and then exposed to an extinction session. The extinction session consisted of two periods: Pre-extinction, 50 trials (same as testing session), and Extinction, 100 trials (no sugar pellet delivered after DS+ press). In each period, the same number of DS+ and DS- trials alternated pseudo-randomly. The number of presses and latency to press after DS+ and DS- were recorded simultaneously with neuronal activity. Animals decreased the number of lever presses during the Extinction period. Neurons in the dmPFC (n= 120) and the VTA (n= 27) responded to DS+, DS- and lever presentation during both Pre-extinction and Extinction periods. However, these responses were different in dmPFC compared to VTA. In the dmPFC, more neurons responded to DS- during Extinction compared to Pre-extinction ($X^2(2)= 6.73$, $p= 0.034$). The number of neurons responding to DS+ was not different in both periods. Critically, different dmPFC neurons responded to DS+ and lever presentation during Pre-extinction compared to

Extinction (30-40% overlap). In contrast to dmPFC, in the VTA, fewer neurons responded to DS+ ($X^2(1)= 3.81$, $p= 0.050$) and DS- ($X^2(1)= 3.97$, $p= 0.046$) during Extinction compared to Pre-extinction. Moreover, the VTA neurons that still responded to DS+ and DS-, and lever presentation during Extinction also responded during Pre-extinction (100% overlap). These results suggest that different neuronal dynamics in response to contextual cues in the dmPFC and the VTA govern the transition to extinction of reward-seeking behavior. *Supported by NIH/NIGMS P30GM122733.*

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.12/EE25

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Ministry of University and Research - NRRP - Grant no. E0000006 - project Mnesys

Title: Mapping the neural correlates of emotional valence attribution: Dissecting circuitry underlying sing-tracking and goal-tracking behaviors

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Abstract: Sensory stimuli, used as conditioned stimuli (CS), can be associated with an intrinsically appetitive stimulus (US), i.e. a reward, through associative learning. Interestingly, there is considerable inter-individual variability in how learning is manifested in animals (and humans): in some cases, CS are endowed with emotional valence and an incentive meaning, becoming strongly attractive/desired, and drive automatic attention and approach, as typical of **sign-tracking**; in others, CS are just memorized as informative reward predictors, as typical of **goal-tracking**. The aim of the current study is to probe major neurocognitive mechanisms underlying evaluative learning via a systematic assessment of varying behavioural phenotypes in the rat model and a characterization of related brain activity. Seventy-eight SD rats, enrolled in a Pavlovian Conditioning Approach paradigm, experienced repeated pairings (30 trials/session) of a retractable lever and a tone (CS) with high-palatable sucrose pellets (US). The protocol comprised 8 sessions, after which rats were perfused to perform brain slicing and processing by immunohistochemistry (IHC) for the brain expression of the immediate early gene c-Fos, and by immunofluorescence (IF) to label neuronal subtypes, including parvalbumin- and calmodulin-positive neurons; analyses were performed via ImageJ and QuPath software. Following a

standardized approach, we quantified any bias in the speed and frequency of rat contacts with the CS or the US at session #8 to classify animals as pure sign- or goal-trackers, or as mixed phenotypes. Results from the PCA paradigm showed radically different behavioral manifestations of evaluative learning in pure phenotypes: along subsequent learning sessions, during CS presentation, sign-trackers developed a strong tendency to quickly and repeatedly approach the cue stimulus; goal trackers, instead, show increased focusing onto the reward location. Based on IHC and IF evidence, pure phenotypes appear to differ in both general activation and neuronal subtype contribution across specific brain regions, including areas within the dopaminergic system, and frontal and sensory cortices, which indicates potentially distinct pathways underlying the two opposing pure behavioral phenotypes. Importantly, modeling patterns of brain activations in critical areas through the whole population of tested animals, including mixed phenotypes, by means of multiple regression analyses, allowed us to significantly explain a substantial portion of the variance in the behavioral manifestations of emotional salience attribution in the context of an evaluative learning paradigm.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.13/EE26

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH

Title: Uncued rewards prevent cortical plasticity during association learning through local serotonin signaling

Authors: *A. RAY[1], Q. LI[2], J. HENDERSON[2], A. L. BARTH[2], J. A. CHRISTIAN[2];
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Abstract: Causal inference is an important function of intelligent systems. Here we investigated how stimulus-reward contingencies modulate input- and target-specific synaptic plasticity in mice learning a whisker-dependent sensory association task (Sensory Association Training; SAT). When the sensory stimulus was perfectly predictive of a water reward during SAT, mice developed strong anticipatory licking to the predictive sensory input and thalamocortical inputs onto L2/3 pyramidal neurons in primary somatosensory cortex (S1) strengthened. When stimulus and rewards were decoupled (pseudoconditioning; PSE), mice neither developed preferential anticipatory licking to the sensory stimulus, nor were the thalamacortical inputs in S1 altered. To identify whether trials with sensory stimulus without reward or uncued rewards were impairing learning, we tested a range of probabilistic stimulus-reward pairings. Uncued rewards potently suppressed stimulus-associated anticipatory licking. Based on these behavioral measurements,

we designed a new training paradigm with uncued rewards (all-reward SAT; AR-SAT) to test its effects on thalamocortical plasticity. AR-SAT prevented both learning and thalamocortical synaptic strengthening, similar to PSE. Unpredicted rewards have been shown to increase serotonergic activity, and serotonin depresses excitatory synapses in sensory cortex. We found that S1 depletion of serotonin during AR-SAT was sufficient to restore thalamocortical plasticity. Thus, unpredicted rewards during AR-SAT suppress thalamocortical synaptic strengthening via serotonin signaling. These data suggest that serotonin signaling is a critical pathway by which uncued rewards reduce causal attribution to unreliable sensory cues.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.14/EE27

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Lateral hypothalamic glutamatergic and GABAergic neurons drive reward or aversion depending on optogenetic stimulation pattern

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Abstract: Lateral hypothalamic glutamatergic and GABAergic neurons drive reward or aversion depending on optogenetic stimulation pattern
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Disclosures Luis Alfredo Rodríguez Blanco: none. Benjamín Arroyo: none. Omar Molina: none Ranier Gutierrez: none.
To guide behavior toward rewards and away from threats or to promote feeding, the lateral hypothalamus (LH) integrates sensory and motivational signals. Although LH GABAergic and glutamatergic populations are known to mediate opposing behavioral valences and bidirectionally modulate feeding, how their real-time activity dynamics drive reward versus aversion and affect feeding remains unclear. Here, we investigated how manipulating these populations with optogenetics shapes behavioral outcomes.We expressed the inhibitory opsin stGtACR2 in the LH of Vglut2-IRES-Cre and Vgat-IRES-Cre mice and delivered light at varying frequencies during a one-bottle test with 10% sucrose. In Vgat-Cre mice, continuous photoinhibition reduced licking relative to controls. In Vglut2-Cre mice, the effect depended on

the light pattern: pulsed photoinhibition at 20 and 50 Hz impaired licking, whereas continuous photoinhibition promoted sustained licking, indicating that stimulation parameters, not the opsin's inhibitory action alone, determine valence.In a brief-access test with 10% sucrose and 2 mM quinine, simultaneous electrophysiological recordings revealed neurons that responded differentially to the two tastants, consistent with encoding of positive and negative valence. In a real-time place preference (RTPP) assay, continuous photoinhibition of Vglut2 neurons produced place preference, whereas pulsed photoinhibition at 5, 10, 20, and 50 Hz elicited frequency-dependent aversion. In Vgat-Cre mice, pulsed photoinhibition at 10 and 20 Hz induced place preference, whereas 5 Hz and 50 Hz did not. During RTPP, in vivo recordings identified distinct glutamatergic ensembles, some with phasic responses to pulsed light and others with activity tied to continuous light, suggesting that spike timing patterns *per se* encode aversive versus rewarding behavior.Together, these results show that LH glutamatergic and GABAergic neurons can drive either reward or aversion, or impair or promote feeding, depending on optogenetic stimulation parameters.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: Research Corporation for Science Advancement Scialog Grant SA-MBC-2024-067a

Title: The role of basolateral amygdala acetylcholine in generating cue-triggered expectations

Authors: *E. RUSSELL, K. M. FRASER;
Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: The basolateral amygdala is essential for updating the predictive value of rewards and encoding stimulus-outcome memories that guide action selection. Cholinergic inputs to the basolateral amygdala are thought to modulate associative learning. For example, optogenetic manipulations of cholinergic afferents to the BLA can alter fear learning and extinction as well as accelerate action-outcome learning. However, how acetylcholine release in the basolateral amygdala contributes to the encoding and utilization of stimulus-outcome associations remains unclear. To address this gap, we implanted rats with cannula targeting the amygdala and pharmacologically manipulated acetylcholine signaling during 1) outcome-specific Pavlovian-to-instrumental transfer (PIT), 2) outcome reinstatement, and 3) outcome devaluation. Long-Evans rats (n=18, 8 male, 10 female) were trained to associate two distinct auditory cues with two distinct reward solutions (sucrose and maltodextrin) and then separately lever press for each

solution. Prior to testing, rats were infused with 0.5 μL of saline, 350 mM scopolamine (a muscarinic receptor antagonist), or 300 mM mecamylamine (a nicotinic receptor antagonist) bilaterally into the basolateral amygdala. Preliminary data suggests that antagonism of basolateral amygdala acetylcholine attenuates outcome-specific PIT. This effect seems attributed to the retrieval of stimulus-outcome memories as we found that scopolamine infusions into the basolateral amygdala blunted stimulus-outcome representations, as indicated by fewer port entries during the cue-period, but also that mecamylamine increased pre-cue entries suggesting receptor-specific control of behavior. Additionally, infusions of mecamylamine blunted cue-elicited port entries during PIT. The results suggest that basolateral acetylcholine plays an important role in modulating cue outcome representations. Additional steps to replicate these findings are ongoing to provide an understanding of basolateral amygdala acetylcholine in the utilization of stimulus-outcome associations to guide adaptive decision-making.

Disclosures: E. Russell: None. **K.M. Fraser:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

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Program #/Poster #: PSTR106.16/EE29

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Intramural Research Program

Title: Selective Activation of D1-MSNs in the Dorsolateral Striatum Alters Novel Object Recognition Without Inducing Hyperlocomotion

Authors: *N. SHARMA[1], S. KANJANDA[2], M. H. SHAH[2], D. M. LOVINGER[2], J. LEE[2]; [1]Natl. Inst. of Hlth., Rockville, MD; [2]NIH, Rockville, MD

Abstract: Within the basal ganglia, dopamine signaling in the striatum is a key regulator of action selection, motivation, reward processing, and novelty-driven behaviors. Consistent with this role, activation of direct pathway D1 receptor-expressing medium spiny neurons (D1-MSNs), either through dopaminergic modulation or optogenetic stimulation, altered operant responding and locomotor activity. However, whether D1-MSN activity also regulates exploratory and cognitive behaviors independently of its effects on locomotion remains largely unknown. Here, we investigated how selective activation of D1-MSNs in the dorsolateral striatum (DLS) influences locomotor activity, dopamine dynamics, and performance in a novel object recognition (NOR) task. EY262-Cre mice received Cre-dependent viral expression of either hM3Dq-mCherry or mCherry in the DLS to selectively target D1-MSNs. Animals were evaluated using a three-day NOR paradigm consisting of open-field exploration (Day 1), familiar object exposure (Day 2), and novel object recognition testing (Day 3). D1-MSN excitability was enhanced by administration of the DREADD agonist Compound 21 (C21). Chemogenetic activation of D1-MSNs did not alter locomotor activity during open-field testing. In contrast,

hM3Dq-expressing mice exhibited significant changes in discrimination index and novel object interaction time compared with mCherry controls, indicating that D1-MSN activation modulates exploratory behavior during object recognition. To determine whether these chemogenetic manipulation effects were accompanied by changes in dopamine signaling, we expressed GRAB-DA in the DLS and performed fiber photometry recordings during DREADD activation of D1-MSNs. Despite the absence of locomotor effects, D1-MSN activation produced a modest elevation in baseline dopamine signals following C21 administration relative to saline treatment. This response differed markedly from pharmacological activation of D1 receptors with SKF81297, which induced robust hyperlocomotion accompanied by pronounced increases in baseline dopamine levels and dopamine transient frequency.Together, these findings demonstrate that selective activation of D1-MSNs in the DLS is sufficient to modulate dopamine tone and novel object interaction without inducing hyperlocomotion. These results suggest that direct-pathway neurons may contribute to exploratory and cognitive processes through mechanisms that are dissociable from their classical role in motor activation.

Disclosures: N. Sharma: None. **S. Kanjanda:** None. **M.H. Shah:** None. **D.M. Lovinger:** None. **J. Lee:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.17/EE30

Topic: H.02. Reward and Appetitive Learning and Memory

Support: BBRF Young Investigator Grant 28187
NIH R01 MH131532-01

Title: Examining the neural mechanisms of location-specific reward learning

Authors: *C. A. SHARP[1], A. BOSSA[1], T. GARG[1], S. DEWITT-BATT[2], B. SUAREZ-JIMENEZ[2];
[2]Neurosci., [1]Univ. of Rochester, Rochester, NY

Abstract: Our ability to learn when and how rewards may be received allows us to ensure our needs are met and maximize our enjoyment of life. Research into the neural underpinnings of this ability has uncovered the mesocorticolimbic pathway as a system comprising structures with key roles in reward processing and learning. However, additional research is needed to examine how people form cognitive maps of where rewards may be present in our environment as we navigate and interact with the world around us. The current research combines fMRI with a virtual task to investigate the neural correlates of location-specific reward learning. Adult participants (n = 30; 14 male) completed a VR reward conditioning task in which they collected asteroids that appeared sequentially in their environment. Asteroids on one half of the environment (the rewarding zone) were paired with “fuel” at a 50% reinforcement rate, as

indicated by an increase in point value and appealing sound, while asteroids on the other half (the non-rewarding zone) were never paired with a reward. After approaching an asteroid, participants were held stationary as they anticipated a possible reward. Voxel analyses are used to examine the effects of time (1st vs 2nd half of the task) and zone (rewarding vs. non-rewarding) on participants' neural activity during the approach and stationary periods. Voxels within the hippocampus, anterior insula, anterior cingulate (ACC), and putamen showed greater activity in the 1st half of the task compared to the 2nd while voxels in the ventromedial prefrontal cortex (vmPFC) showed the opposite ($p < .05$ FDR-corrected). Voxels within the ACC also showed greater activity in the non-rewarding zone compared to the rewarding zone ($p < .001$) whereas voxels within the orbitofrontal cortex (OFC), caudate, and dorsomedial prefrontal cortex (dmPFC) showed greater activity in the rewarding zone, compared to the non-rewarding zone, specifically in the 2nd half of the task ($p < .001$). During the stationary period, the anterior insula, OFC, dmPFC, and putamen showed greater activity in the 1st half of the task, compared to the 2nd, and voxels of the OFC and vmPFC showed greater activity in the non-rewarding, compared to rewarding, zone ($p < .001$). These findings support unique roles of components of the mesocorticolimbic pathway in forming a cognitive map of where in our environment we are more likely to encounter a reward. Future research can investigate how the recruitment of these regions may differ in individuals with reward processing-related psychopathologies to refine our understanding of the neurobiology of these disorders and inform our development of effective treatments.

Disclosures: C.A. Sharp: None. **A. Bossa:** None. **T. Garg:** None. **S. DeWitt-Batt:** None. **B. Suarez-Jimenez:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.18/EE31

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Hacettepe University TSA-2020-18753
Hacettepe University THD-2024-21438

Title: Layer-, input-, susceptibility-specific synaptic organization of ACC neurons

Authors: *T. SOLAKOGLU[1], E. ERDENER[2], O. GLIKO[3], A. CAN[4], U. SÜMBÜL[3], E. EREN KOCAK[2];
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Abstract: Introduction: Chronic stress reduces dendritic branching and spine density in dendrites of anterior cingulate cortex (ACC). Identifying the region origin and dendritic organization of synaptic inputs is critical to understand how chronic stress alters ACC function. Here, we mapped excitatory synapses from ventral tegmental area (VTA), ventral hippocampus (VH), and basolateral amygdala (BLA) onto ACC pyramidal neurons (E-to-E) and interneurons (E-to-I) and compared synaptic connectivity profiles between stress-naive (SN), stress-susceptible (SS) and stress-resilient (SR) mice.**Methods:** Synapses were labeled using enhanced green fluorescent protein reconstitution across synaptic partners (eGRASP) in 24 male C57BL/6 mice. AAVs expressing cyan, green, or yellow pre-eGRASP under CaMKII promoter were injected into VTA, VH, and BLA, respectively. AAVs expressing post-eGRASP under either CaMKII promoter or mDlx enhancer were injected into ACC. Three weeks later, mice were exposed to chronic social defeat stress for 10 days. On day 11, mice were classified as SS or SR via social interaction test. High resolution, frame sequential, 3D confocal tile scans and automated algorithms were used to detect synapses. We quantified numbers and spatial distribution of synapses and their dendritic segments.**Results:** We mapped >165,000 synapses on >500,000 dendritic segments across ACC. Among E-to-E synapses, SS mice showed a reduction in the ratio of VH synapses and increase in the ratio of BLA synapses to all detected synapses in layer 5b and layer 6. A similar shift was observed at segment level, with reduced numbers of segments with only VH inputs and increased numbers of segments with only BLA inputs to all segments. In layer 6, SS mice also showed an increase in the proportion of dendritic segments receiving inputs from multiple brain regions. Among E-to-I synapses, stress-exposed mice showed an increase in the proportion of VTA synapses in layer 5b and layer 6. SS mice showed a decrease in the proportion of VH synapses in layer 6.**Conclusion:** We revealed a stress-susceptibility dependent shift in ACC synaptic input profile that includes both layer and cell specific redistribution of inputs across cortical layers and increased diversity of input combinations on individual dendritic segments, particularly in deep-layer ACC. While VH and BLA inputs may control excitation-inhibition balance, VTA inputs may modulate ACC dynamics during chronic stress. Going forward, maps with I-to-E and I-to-I synapses and computational modeling will help determine how neuron type, layer, and input specific synaptic reorganization contribute to altered ACC function in chronic stress.

Disclosures: T. Solakoglu: None. **E. Erdener:** None. **O. Gliko:** None. **A. Can:** None. **U. Sümbül:** None. **E. Eren Kocak:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.19/EE32

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Amygdala circuits contribute to olfactory reward learning

Authors: *L. TAN[1], L. CUI[2], X.-M. LI[3];
[1]Sch. of Brain Sci. and Brain Medicine, Zhejiang Univ., Hangzhou, China; [2]Zhejiang Univ., Hangzhou, China; [3]Inst. of Neurosci., Hangzhou, China

Abstract: Olfactory reward learning is crucial for food identification and foraging behavior in complex environments, representing a fundamental and evolutionarily conserved ability in animals. However, how specific amygdala-related circuits encode reward-associated olfactory cues during olfactory reward learning remains unclear. To address this question, we used an appetitive olfactory conditioning paradigm in which a neutral odor was paired with a 10% sucrose reward, inducing conditioned odor-evoked approach behavior. Using targeted neuronal ablation, we found that VGLUT1-positive neurons in the basolateral amygdala are necessary for olfactory reward learning. In addition, viral tracing combined with fiber photometry calcium recordings in freely moving mice revealed that a specific neuron population within the amygdala showed enhanced responses to the sucrose reward and reward-associated odor cues. Together, these results suggest that this amygdala-related circuit participates in assigning acquired motivational value to olfactory cues.

Disclosures: L. Tan: None. **L. Cui:** None. **X. Li:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.20/FF1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Intramural Research Award
NIH Center on Compulsive Behaviors Graduate Student Fellowship

Title: Novel long-range projecting GABAergic hippocampal-septal somatostatin neurons across species

Authors: *A. VLACHOS[1], N. MCLEAN[1], A. CACCAVANO[2], V. K. CHITTAJALLU[1], G. A. VARGISH[3], L. T. HEWITT[3], X. YUAN[1], S. HUNT[1], E. FURLANIS[4], Y. WANG[4], M. DAI[4], J. WU[4], A. C. PEREIRA[4], J. DIMIDSCHSTEIN[4], M. A. ELDRIDGE[5], B. B. AVERBECK[5], G. J. FISHELL[4], K. A. PELKEY[1], C. J. MCBAIN[1];
[1]NICHD/NIH, Bethesda, MD; [2]NICHD/NIH, Washington, DC; [3]Section on Cell. and Synaptic Physiol., NICHD/NIH, Bethesda, MD; [4]Broad Inst., Boston, MA; [5]NIMH/NIH, Bethesda, MD

Abstract: GABAergic inhibitory interneurons (INs) are a notoriously heterogenous population that are imperative for regulating information flow and processing amongst glutamatergic neurons of forebrain circuits. Discrete IN subtypes emerging from advanced transcriptomic clustering require detailed anatomical, molecular, and functional characterization to better understand the cellular components of cognitive processes underlying behavior. Furthermore, while IN diversity is best characterized in rodents, the degree of conservation of discrete IN

subpopulations in higher species is understudied but required to understand human brain function in health and disease. Using a novel cell-type specific labelling adeno-associated virus (HPSE cis-acting regulatory enhancer, BiSSTe10) injected into the hippocampus of mice and macaques, we discovered a subpopulation of hippocampal somatostatin INs with unique molecular, anatomical, and electrical properties. In both species, BiSSTe10 labeled neurons co-stain for somatostatin but not parvalbumin. Acute slice patch clamp recordings of BiSSTe10 cells in both mouse and macaque hippocampal reveal two electrophysiologically distinct subpopulations in the stratum oriens, with firing profiles inclusive of regular-spiking (<100 Hz) and fast-spiking (>200 Hz) maximum sustained firing frequencies. Additionally, all cells exhibit voltage sag at the onset of a hyperpolarizing step, indicative of HCN-channel conductance. Whole brain tissue clearing in mice reveals that, in addition to local hippocampal axons, BiSSTe10 cells form extrahippocampal projections to the medial septum and ventral diagonal band (MSvDB). Optogenetic activation of BiSSTe10 axons show GABAergic input onto MSvDB cells in slice recordings, with some target selectivity for MSvDB INs. In HPSE-Cre labeled mice, HPSE+ CA1 hippocampal cells reveal similar electrophysiology to regular-spiking BiSSTe10+ cells and project to the MSvDB, an anatomical divergence from the neocortical HPSE somatostatin cells. *In vivo* calcium activity of BiSSTe10 cells in behaving mice is positively correlated with locomotion, suggesting activation of BiSSTe10 cells during theta oscillations, which are reported across the hippocampal-septal circuit. Collectively, these data suggest hippocampal BiSSTe10 neurons are unique from previously described hippocampal-septal projecting GABAergic neurons and are poised to contribute to hippocampal-septal dialogue during network oscillations. Importantly, these neurons are evolutionarily conserved across species, indicating their potential role in higher order neural circuits and human disease.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.21/FF2

Topic: H.02. Reward and Appetitive Learning and Memory

Title: The cellular origins of MFB reward signals: closing in on the quarry of a seven-decade hunt

Authors: *J. VOISARD, A. ARVANITOGIANNIS, P. SHIZGAL;
Concordia Univ., Montréal, QC, Canada

Abstract: The directly activated neurons that give rise to the powerfully rewarding effect of medial forebrain bundle (MFB) stimulation have yet to be identified despite over seventy years of intensive search. Although MFB self-stimulation depends on dopamine transmission, the rewarding effect arises primarily from direct activation of non-dopaminergic neurons. Evidence from psychophysical, electrophysiological and lesion studies suggests that the somata of at least some of the directly activated neurons are in the basal forebrain. When rats work for direct optical activation of midbrain dopamine neurons, dopamine-transporter blockade reduces the stimulation strength required to produce a reward of given intensity. In contrast, when rats work for electrical MFB stimulation, the required stimulation strength remains roughly constant in the face of dopamine-transporter blockade, but the rats are willing to pay higher opportunity costs to earn a reward of given strength. We expressed ChR2 or ChroME2f in basal forebrain neurons and implanted optical fibers at classical MFB-stimulation sites. Optical stimulation in these rats was highly rewarding: The rapid acquisition of the operant response and its vigorous performance were reminiscent of what is observed in rats working for electrical MFB stimulation. In rats expressing ChR2, the effectiveness of the optical stimulation grew steadily as the pulse frequency was increased to values of ~70 Hz. With the opsin ChroME2f, effectiveness increased up to pulse frequencies of ~120 Hz, a value that may reflect the limits of the opsin more than the limits of the axons. The effect of dopamine-transporter blockade paralleled the results obtained in rats working for electrical MFB stimulation: willingness to pay opportunity costs increased, but the stimulation strength required to produce a reward of given intensity remained roughly constant. These findings implicate non-dopaminergic, MFB-projecting basal forebrain neurons in the directly stimulated stage of the MFB reward substrate.

Disclosures: J. Voisard: None. **A. Arvanitogiannis:** None. **P. Shizgal:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.22/FF3

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NSF GRFP
R01MH127214
T32 MH073526
NARSAD Young Investigator Award from BBRF
F30MH134633

Title: Retrosplenial circuit refinement promotes the developmental emergence of persistent memory

Authors: *A. L. YU, B. JIN, M. GONGWER, B. P. KEARNEY, A. DARMAWAN, L. HOLDEN-WINGATE, S. RUEDA, L. A. DENARDO;
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Abstract: Memories formed early in life are rapidly forgotten, whereas those formed later persist. Recent work revealed that physical traces of infant memories endure in the brain but are inaccessible to natural recall. However, the developmental processes regulating this transition remain unclear. Here, we performed a brain-wide developmental screen, revealing age-dependent shifts in regional activation patterns that parallel the emergence of stable memory expression. We focused on the retrosplenial cortex (RSP)—a critical region for adult memory consolidation with poorly understood developmental roles—as a candidate whose refinement may influence memory recall. Persistent memory aligned with increased reactivation of RSP ensembles and dendritic spine refinement. Reactivation of RSP infant learning ensembles a month, but not a week, after learning reinstated forgotten memories, coinciding with dendritic spine refinement on those cells. These findings reveal the developmental trajectory of the RSP, uncovering key maturation features that align with the transition from forgetting to remembering.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.23/FF4

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Evolutionary rise of a synaptic mechanism for creating and diversifying key reinforcement signals

Authors: *S. SHABEL[1], L. RIOS[2], V. RYBALCHENKO[3];
[1]UTSW, Dallas, TX; [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Most neurons release either excitatory or inhibitory neurotransmitters. However, in the lateral habenula (LHb), multiple inputs co-transmit glutamate and GABA - transmitters with opposing effects on LHb output. Although the LHb has an established role in reinforcement learning, the adaptive significance of glutamate/GABA co-release in the LHb remains unclear. Here we use machine learning image classification and analysis of scRNA-seq datasets to show that co-release of GABA with glutamate proliferated and expanded during evolution (fish < mice < rats < monkeys) in mammalian LHb circuits. Neural simulations show that GABA co-release with glutamate is sufficient to produce temporal difference (TD) - like transformations of input activity - a computation that is commonly used for reinforcement learning and behavioral optimization. Heterogeneous GABA-to-glutamate co-transmission ratios, like those found among LHb neurons ex vivo, produce diverse TD-like computations, which have been linked to higher-order decision-making. Consistent with predictions from the simulations, reduction of GABA co-release in glutamatergic afferents to the LHb reduces risky decision-making in mice. Proliferation of a synapse able to produce and diversify such critical computations may have

aided the evolution of sophisticated learning and decision-making that contribute to intelligent behavior.

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Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.24/Web Only

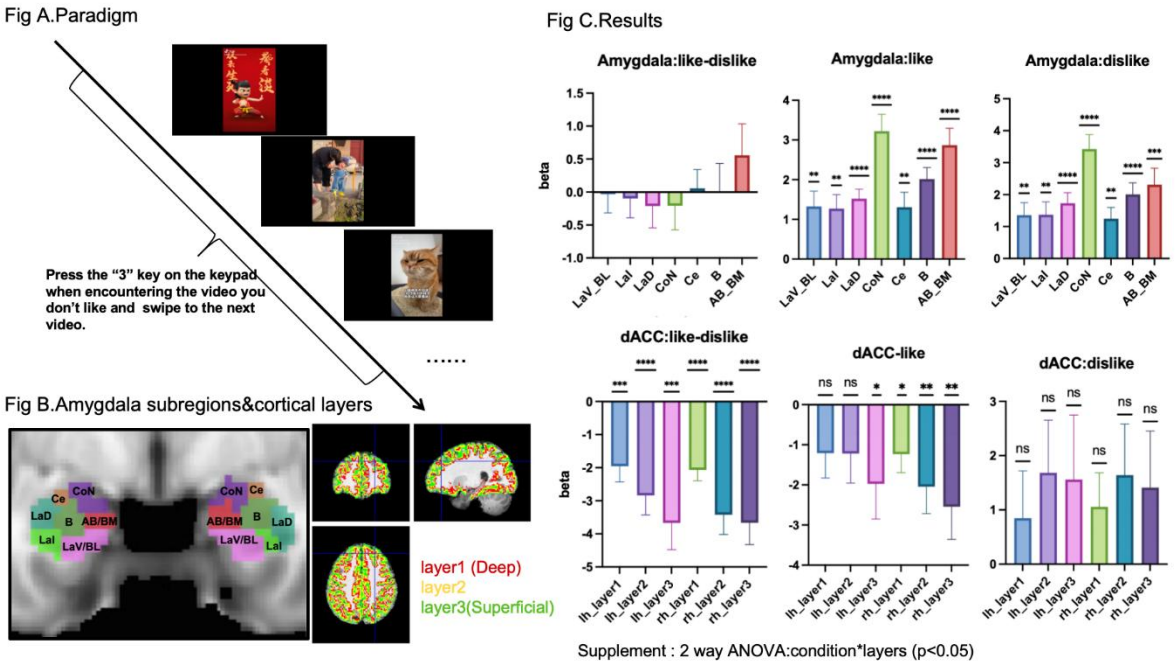
Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Natural Science Foundation of China (No. 81971245, 82501790, 82471511)

Title: Amygdala subregion activation and laminar dACC suppression during naturalistic free short-video viewing: a 7T fMRI study

Authors: *R. WANG, H. ZHOU, Y. HU;
Zhejiang Univ., Hangzhou, China

Abstract: Short videos are characterized by personalized content and high sensory salience, making them highly immersive and difficult to disengage from. During immersive viewing, top-down control systems are suppressed while automatic fast-response emotional systems are strongly activated — a pattern that may help explain why stopping feels so difficult. Yet the subregional and laminar architecture underlying these responses has not been examined.We recorded 7T fMRI data from N=27 participants who freely watched short videos in the scanner. Preference was indexed behaviorally: a video watched to completion counted as "liked"; one abandoned early, as "disliked." BOLD responses were analyzed across seven amygdala cytoarchitectonic subregions (LaV, La, Lb, Ca, B, AB, M) and three depth-equidistant cortical layers of dACC.All amygdala subregions were significantly activated under both conditions, and the direct like-versus-dislike contrast yielded no significant differences — though response magnitudes varied across subregions. The dACC told a different story: liked videos drove significant negative activation in several cortical layers, while disliked videos produced only weak, non-significant positive responses. The like-minus-dislike contrast showed significant suppression across all dACC layers, and a significant condition × layer interaction confirmed that suppression depth varies with cortical depth.Amygdala subregions showed robust activation under both conditions with no significant preference-dependent differences at subregional resolution, though response magnitudes varied across subregions.The stronger dACC suppression during liked videos, by contrast, points to a preference-dependent withdrawal of top-down control — lending neural specificity to the idea that immersive short-video viewing selectively disengages the control system. 7T fMRI resolves this suppression at laminar resolution, revealing a depth-dependent organization that standard field strengths cannot access.



Disclosures: R. Wang: None. **H. Zhou:** None. **Y. Hu:** None.

Poster

PSTR106: Circuit Motifs of Reward: Amygdala, Habenula, Hippocampus, and Beyond

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR106.25/FF5

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant R00DA057390

Title: Ventral pallidum functional and neuroplastic regulation of the predictive versus incentive motivational value of a reward-paired cue

Authors: *P. PAKALAPATI[1], B. N. KUHN[2], A. BERCKMUELLER[3];
[1]Psychology and Neurosci., [2]Dept. of Neurosci., [3]Baylor Univ., Waco, TX

Abstract: The ventral pallidum (VP) is the main output structure of the nucleus accumbens core and mediates several complex motivated behaviors, including appetitive and aversive cue-reward relationships. However, it is unknown what aspect of the cue-reward relationship the VP regulates. Using the sign-tracker (ST)/goal-tracker (GT) model we can parse the predictive versus incentive motivational value of a reward-paired cue. In this paradigm, rats undergo Pavlovian Conditioned Approach training whereby an illuminated lever (conditioned stimulus,

CS) precedes the delivery of a food pellet (unconditioned stimulus, US). Despite all rats learning the non-contingent relationship between the lever-CS and food-US pairing, two distinct conditioned responses emerge. STs vigorously engage with the lever-CS during presentation whereas GTs orient toward the location of food-US delivery. STs will also work harder for presentation of the lever-CS during a test for conditioned reinforcement (CRT). Within this model, GTs attribute a predictive value to the lever-CS whereas STs attribute an incentive motivational value. The VP is necessary for the acquisition of a sign-tracking response; however, it is unknown if it is necessary for the expression of the motivational value of the lever-CS. Using the ST/GT model, we are assessing how the VP mediates the expression of the predictive versus the incentive motivational value of a reward-paired cue during the CRT. Using male and female Sprague-Dawley rats, we successfully phenotyped rats as ST, GT, or having an intermediate phenotype. Using c-fos protein as a marker of neuronal activity, preliminary data suggests the VP contributes to the expression of the incentive motivational properties of the lever-CS. Current analyses are using inhibitory and stimulatory DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) to bidirectionally manipulate the VP during the CRT in STs and GTs. We expect STs to work less for lever presentation when the VP is inhibited and for both STs and GTs to show increased levels when the VP is stimulated. Quantification of perineuronal nets, a component of the extracellular matrix that regulates motivated states, is also underway to better characterize how VP neuroplastic adaptations contribute to the incentive motivational value of a reward-paired cue. Future work will identify and examine how VP neurocircuits contribute to these effects. Using a model of individual variation in the predictive versus incentive motivational value of a reward-paired cue, we can more definitively characterize the functional and neuroplastic contribution of the VP to cue-reward expression.

Disclosures: P. Pakalapati: None. **B.N. Kuhn:** None. **A. Berckmueller:** None.

Poster

PSTR107: Neural Circuits for Reward, Value, and Motivated Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.01/FF6

Topic: H.03. Motivation

Support: JSPS KAKENHI Grant JP26H01986
JSPS KAKENHI Grant JP25H02499
JSPS KAKENHI Grant JP24H02164
JSPS KAKENHI Grant JP24K21499
JSPS KAKENHI Grant JP23K25753
JST FOREST Program JPMJFR2040
JSPS KAKENHI Grant JP25K00895
JSPS KAKENHI Grant JP23K18420

Title: Distinct dopamine signals support state-dependent behavioral adjustment toward future rewards

Authors: *S. ISHINO[1], R. TSUKASA[2], H. KAWAMURA[1], M. OGAWA[1];
[1]Shiga Univ. of Med. Sci., Shiga, Japan; [2]Kyoto Univ., Kyoto, Japan

Abstract: The ability to sustain actions toward future rewards is fundamental to adaptive behavior. Reward pursuit often requires animals to cope with repeated nonreward by flexibly adjusting their actions according to the current task state. How the dopamine system supports this state-dependent behavioral adjustment remains poorly understood. Canonical dopamine (DA) neurons in the lateral ventral tegmental area (VTA), termed Type 1 neurons, are thought to encode reward prediction errors (RPEs). Because these neurons decrease their activity when expected rewards are omitted, Type 1 signals alone cannot readily explain how animals sustain reward pursuit through repeated nonreward. We previously identified Type 2 DA neurons in the lateral VTA, which show response properties opposite to those of Type 1 neurons, increasing after reward omission and decreasing after reward delivery. Here, we examined how Type 1- and Type 2-related DA signals in the nucleus accumbens (NAc) support state-dependent behavioral adjustment during sustained reward pursuit. Head-restrained rats performed an operant task in which they manipulated a lever to obtain reward only after three consecutive unrewarded trials. Using fiber photometry with the DA sensor GRAB-DA2m, we simultaneously recorded DA signals from the lateral NAc, likely reflecting Type 1-related input, and the anterior NAc, likely reflecting Type 2-related input, across learning. This allowed us to relate DA dynamics to trial-by-trial lever trajectories. Lateral NAc DA signals were consistent with RPEs, whereas anterior NAc DA signals showed distinct learning-dependent dynamics. Around transitions to the next trial after nonreward, anterior NAc DA signals showed phasic increases. During the inter-trial interval, anterior NAc DA signals increased stepwise as animals approached the rewarded trial. These signals were related to the mismatch between the ongoing lever trajectory and the action expected from the inferred current task state. These results suggest that Type 1 and Type 2 DA systems carry distinct but complementary signals associated with state-dependent behavioral adjustment, allowing animals to sustain reward pursuit through repeated nonreward.

Disclosures: S. Ishino: None. **R. Tsukasa:** None. **H. Kawamura:** None. **M. Ogawa:** None.

Poster

PSTR107: Neural Circuits for Reward, Value, and Motivated Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.02/FF7

Topic: H.03. Motivation

Support: NIH Grant R00MH130688
Whitehall Foundation Fellowship

Title: Differential Reinforcing Effects of Region-Specific Dopamine Populations

Authors: *S. T. ZDON, A. KALONJI, S. M. WARLOW;
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: While the role of ventral tegmental area (VTA) dopamine neurons in reward-related motivation has been well established, the role of other dopamine populations such as in the dorsal raphe nucleus (DRN) remains unclear. Here, we examined how VTA and DRN dopamine populations, which have differential projection patterns, contribute to reward and aversion. To target dopamine neurons, we expressed a Cre-dependent Channelrhodopsin-2 (ChR2) in the VTA or DRN of DAT-Cre mice. We first tested the inherent reinforcing properties of stimulating dopamine neurons in VTA (VTA^{DA}) vs. DRN (DRN^{DA}) using a 2-nose poke intracranial self-stimulation (ICSS) assay that offers optogenetic laser stimulation upon successful nose poking. We found that VTA^{DA} stimulation was highly reinforcing among a sub-population of mice, while mice were indifferent to DRN^{DA} stimulation. We then used a real-time place procedure to assess reinforcing or aversive properties of stimulation. Similar to ICSS results, VTA^{DA} mice showed a strong preference for the laser-paired compartment, while DRN^{DA} mice showed no preference or avoidance. We next tested the ability for VTA^{DA} vs. DRN^{DA} to modulate ongoing motivation for natural rewards such as sucrose. DRN^{DA} stimulation did not alter ongoing motivation for sucrose, while VTA^{DA} stimulation amplified sucrose motivation among the self-stimulators. Finally, we tested whether either dopamine population contributes to fear learning. We found that DRN dopamine may enhance, while VTA dopamine may suppress fear learning. Our results show differential reinforcing effects of region-specific dopamine populations, suggesting distinct roles of dopamine across mesolimbic circuitry.

Disclosures: S.T. Zdon: None. **A. Kalonji:** None. **S.M. Warlow:** None.

Poster

PSTR107: Neural Circuits for Reward, Value, and Motivated Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR107.03/FF8

Topic: H.03. Motivation

Support: NIH Grant R00MH130688

Title: VTA neurons that co-release GABA and glutamate encode for motivational salience, but not valence

Authors: *M. Y. COURTNEY, A. NGUYEN, V. COBB, S. M. WARLOW;
Psychological and Brain Sci., Dartmouth Col., Hanover, NH

Abstract: The ventral tegmental area (VTA) mediates reward and threat-related motivation, most notably through its dopamine neurons. Yet, the VTA is a heterogenous structure with several different cell types each of which can also promote motivated behavior. Within the VTA, a subset of neurons has the capacity to co-release multiple neurotransmitters, including a population that can co-release GABA and glutamate. The functional role of these neurons in motivated behavior remains less understood. Here, we aimed to understand how VTA GABA/glutamate neurons encode for reward- or threat-related motivation. To target this co-

releasing population, we expressed a Cre- and Flp-dependent calcium indicator (GCaMP6f) into the VTA of dual VGAT-Flp/VGLUT2-Cre mice. Mice first underwent Pavlovian reward conditioning. Consistent with prior work, we found that VTA GABA/glutamate activity increased during sucrose reward delivery, but was not modulated by cue presentation, either before or after learning. We then assessed how VTA GABA/glutamate neurons encode for either passive or active forms of threat learning using a Pavlovian fear conditioning task and a novel shock probe defensive burying task. We found that shock delivery, but not a shock-associated cue, modulates VTA GABA/glutamate activity. Overall, our results suggest that VTA GABA/glutamate neurons encode for the motivational salience of stimuli, rather than valence or their associated cues, a unique role distinct from that of VTA dopamine neurons. These findings highlight a novel cell population capable of promoting reward or threat related motivation, which may be dysregulated in neuropsychiatric diseases involving imbalanced motivation such as addiction or depression.

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Poster

PSTR107: Neural Circuits for Reward, Value, and Motivated Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR107.04/FF9

Topic: H.03. Motivation

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Title: Distinct Lateral VTA Dopamine Neuron Subtypes Show Opposing Responses to Reward-Predicting Cues and Outcomes

Authors: *H. KAWAMURA, S. ISHINO, M. OGAWA;
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Abstract: Adaptive behavior often requires animals to maintain engagement when expected rewards are uncertain, delayed, or omitted. Dopamine (DA) neurons in the lateral ventral tegmental area (VTA) are known to signal reward prediction error (RPE; Type 1 neurons), increasing activity to better-than-expected outcomes and decreasing activity when outcomes are worse than expected. However, our previous work identified a DA neuron population (Type 2 neurons) whose responses are opposite to classical RPE-coding Type 1 neurons, with increased

activity following reward omission and decreased activity in response to reward delivery (Ishino et al., 2023). This suggests that lateral VTA DA neurons convey distinct signals beyond the conventional RPE frameworks, particularly under uncertain reward conditions. To further characterize Type 2 DA neurons, we performed single-cell calcium imaging of lateral VTA DA neurons in head-restrained rats during instrumental and Pavlovian conditioning paradigms. In the instrumental probabilistic task, three auditory cues predicted reward with 100%, 50%, or 0% probability. Type 1 neurons exhibited positive cue responses that scaled with reward probability. In contrast, more than half of Type 2 neurons showed increasingly negative cue responses at higher reward probabilities, revealing an inverted cue-scaling pattern. This opposing pattern was also observed during Pavlovian conditioning using the same reward-probability structure but without instrumental action requirements. We next examined how cue- and outcome-related responses changed across learning. In both Type 1 and Type 2 neurons, cue responses attenuated in later learning phases, whereas outcome responses were largely maintained, suggesting that reward-related information may not be uniformly transferred from outcomes to predictive cue signals across learning. Type 2 neurons also showed comparatively weak and more heterogeneous responses to cues predicting an aversive air-puff and to the air-puff outcome, despite their robust suppression by reward-predicting cues and reward delivery. Thus, Type 2 neurons may be preferentially suppressed by reward-predicting cues and outcomes rather than activated by aversive events. Taken together, these results reveal a functional dissociation within lateral VTA DA systems, whereby Type 1 and Type 2 neurons show opposing response patterns to reward-related cues and outcomes.

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Poster

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Support: NIH Grant R01DA044315
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Title: Dopamine neuron synchronization is critical for state-dependent value encoding

Authors: *S.-W. JIN, M. X. BERNSTEIN, O. KOITA, M. TRZECIAK, L. S. ZWEIFEL; Univ. of Washington, Seattle, WA

Abstract: Ventral tegmental area (VTA) dopamine (DA) neurons are known to encode the value of rewarding stimuli. However, these neurons differentially encode water-predicting and food-predicting cues under thirst or hunger conditions. The difference in this state-dependency may be explained by the dense expression of receptors for peptide hormones and neuropeptides linked to

feeding regulation, such as ghrelin, orexin (Orx), and neurotensin (Nts), but not for peptide receptors linked to thirst, like angiotensin II or vasopressin. The molecular mechanisms for internal states regulation of DA neuron activity by neuropeptides remain largely unknown. Here, we focused on the non-selective cation channel transient receptor potential channel 6 (Trpc6) as a potential key regulator of VTA DA neurons downstream of neuropeptide regulation of state-dependent value encoding. The feeding-related peptides, ghrelin, Nts, and Orx signal through Gq-coupled receptors that generate diacylglycerol (DAG) which has been shown to directly activate Trpc6 channels. Consistent with this idea, our preliminary data demonstrate that Trpc6 is coupled to peptidergic GPCRs, such as ghrelin and Nts receptors, but not to GPCRs for glutamate and acetylcholine receptors. To determine the contribution of Trpc6 to state-dependent value encoding, we selectively mutagenized the genes encoding either *Trpc6* (n = 6) or *Rosa26* (control, n = 5) in dopamine neurons using a viral-mediated CRISPR/SaCas9 strategy. To visualize single-cell dopamine neuron activity dynamics, we then implanted a microprism adjacent to the VTA and performed in vivo two-photon calcium imaging. Then, head-fixed mice were tested under water-restricted or food-restricted conditions in a counter-balanced fashion and presented with five sucrose solutions (0% to 30%) in a pseudorandom order. Our results showed that, under food restriction, DA neurons in the *Trpc6*-mutagenized group exhibited reduced scaling of activity across sucrose concentrations and decreased synchronization during sucrose consumption compared to control mice. In contrast, no significant differences were observed between groups under water restriction. We next examined how dopamine neurons in *Trpc6*-mutagenized mice respond during a Pavlovian conditioning task under food restriction. In these mice, DA neurons in the Trpc6 group exhibited impaired synchronized activity in response to reward delivery compared to control mice and displayed deficits in outcome devaluation. Taken together, our findings demonstrate that Trpc6 plays a critical role in encoding reward value and contributing to synchronized dopamine neuron activity under hunger states.

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Poster

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Topic: H.03. Motivation

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Title: Differential Influences of Ventral Tegmental Area Dopaminergic Neuron Subtypes During Associative Learning

Authors: *S. K. IKENBERRY, G. A. AIMALE, D. H. ROOT;
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Abstract: Dopaminergic neurons of the Ventral Tegmental Area (VTA) are highly involved in the regulation of motivated behaviors such as reward-seeking or aversion-avoidance. In humans, VTA function is associated with addiction, schizophrenia, depressive disorders, cognitive decline in ageing, behavioral disorders, and more. VTA dopamine neurons are molecularly heterogeneous, with two prominent populations differing in neurotransmitter release. One dopaminergic subpopulation, defined by dopamine synthesis via tyrosine hydroxylase (TH) and expression of the Vesicular Glutamate Transporter 2 (VGluT2), co-transmits glutamate and dopamine (glutamate-dopamine neurons). A second subpopulation expresses TH but not VGluT2, synthesizing and transmitting dopamine without glutamate (nonglutamate-dopamine neurons). We have previously shown that glutamate-dopamine and nonglutamate-dopamine neurons differ in their axonal targets and somatic neuronal activity in both rewarding and aversive contexts in well-trained mice. However, whether these neurons differ over the course of reward and aversion-related associative learning is unknown. We investigated the roles of glutamate-dopamine neurons and non-glutamate dopamine neurons during Pavlovian associative learning and extinction learning. VGlut2::Cre/TH::Flp mice (n=23, 8-12 weeks, 12F 11M) were injected with the calcium indicator GCaMP6m targeting VGluT2+TH+ (glutamate-dopamine) neurons (n=11), or VGlut2-TH+ (non-glutamate dopamine) neurons (n=12) in the VTA, and an optic fiber was implanted above the cell populations of interest. Mice then underwent associative reward and fear conditioning, followed by cued extinction learning in the absence of rewarding or aversive outcomes. Daily fiber photometry recordings of calcium activity at the soma of VTA dopaminergic neurons show distinct patterns of activity between the two populations, suggesting differential influence in reward and aversion learning. We interpret these results such that VTA dopaminergic involvement in learning and VTA-related disorders involving learning, such as addiction, schizophrenia, Parkinson's disease, or Alzheimer's disease, may depend on the influence of unique dopaminergic sub-cell types.

Disclosures: S.K. Ikenberry: None. **G.A. Aimale:** None. **D.H. Root:** None.

Poster

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Topic: H.03. Motivation

Support: NIH Grant 5R01MH137472-03

Title: Ventral Tegmental Area Glutamate-Dopamine and NonGlutamate-Dopamine Neuronal Activity During Sequential Conditioning Learning

Authors: *G. A. AIMALE, S. K. IKENBERRY, D. H. ROOT;
Univ. of Colorado Boulder, Boulder, CO

Abstract: Dopamine (DA) plays important roles in reward, learning, and motivation. One widely supported hypothesis of dopamine's role in learning is the reward prediction error hypothesis. However, other hypotheses regarding dopamine's function have been proposed, such as incentive salience and adjusted net contingency for causal relations (ANCCR). Within the Ventral Tegmental Area (VTA), two prominent dopaminergic subpopulations differ in neurotransmitter release. One dopaminergic subpopulation defined by dopamine synthesis via tyrosine hydroxylase (TH) and expression of the Vesicular Glutamate Transporter 2 (VGluT2) co-transmits glutamate and dopamine (glutamate-dopamine neurons). A second dopaminergic subpopulation expresses TH without VGluT2 co-expression and transmits dopamine without glutamate (nonglutamate-dopamine neurons). We previously observed differing signaling patterns between glutamate-dopamine neurons and nonglutamate-dopamine neurons in the VTA during Pavlovian reward and aversion learning paradigms. However, whether either cell-type signals more or less consistent with different dopaminergic theories is unknown. To investigate this, we utilized transgenic mice (VGluT2::Cre/TH::FlpO mice, n = 18, 8-12 weeks, 11F 7M), and injected AAVs encoding the calcium indicator GCaMP6m into either glutamate-dopamine (VGluT2+TH+, n = 10 mice) or nonglutamate-dopamine (VGluT2-TH+, n = 8 mice) neurons of the VTA. Following the injection, we implanted an optic fiber directly above the targeted cell population. Utilizing fiber photometry, daily calcium recordings were obtained from the respective VTA DA neuron subtypes. Mice performed a sequential conditioning task involving a cue (CS1) predicting a second cue (CS2) that then sequentially predicts a sucrose reward. Uniquely, reward prediction error, incentive salience, and ANCCR theories of dopamine function posit differential task sensitivity. We hypothesized that DA subtypes may signal differentially according to different theories of dopamine function. Initial behavioral tests observed more responding during CS2 than CS1 consistent with prior sequential conditioning examinations. However, additional behavioral tests suggested that mice interpret sequential cues differently than previously assumed. We also observed distinct calcium signaling dynamics in the two DA subpopulations related to sequential cues. We interpret these data such that one singular DA hypothesis cannot fully encapsulate the heterogenous dynamics of genetically-distinct VTA DA subpopulations.

Disclosures: G.A. Aimale: None. **S.K. Ikenberry:** None. **D.H. Root:** None.

Poster

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Program #/Poster #: PSTR107.08/FF13

Topic: H.03. Motivation

Support: Intramural Research Program of the National Institute on Drug Abuse

Title: A GABAergic pathway from the Substantia Nigra pars reticulata to the Dorsal Raphe regulates feeding and risk-seeking behaviors

Authors: *M. BARBANO, H.-L. WANG, U. MOHAMMAD, O. ESPINOZA, M. F. MORALES;
Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Although the dorsal raphe nucleus (DR) is primarily recognized for its serotonergic population, it also contains glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGluT3). We previously showed that DR-VGluT3 neurons establish excitatory monosynaptic connections with a subset of ventral tegmental area (VTA) dopamine neurons projecting to the nucleus accumbens, and that activation of this pathway promotes reinstatement of cocaine-seeking behavior. To identify afferent circuits controlling DR-VGluT3 neurons, we performed retrograde tracing and found a prominent input from GABAergic neurons expressing the vesicular GABA transporter (VGaT) in the Substantia Nigra pars reticulata (SNr). To investigate the behavioral function of this SNr-DR pathway, VGaT-Cre mice received SNr injections of viral vectors encoding channelrhodopsin-2 (ChR2), halorhodopsin (Halo), or enhanced yellow fluorescent protein (eYFP), and optical fibers were implanted above the DR. By combining optogenetic manipulations with behavioral assays we found that activation of SNr GABAergic terminals in the DR reduced anxiety-like behavior, an effect abolished by GABA receptor antagonists. Stimulation of this projection also attenuated depression-like behavior while increasing risk-seeking responses. Conversely, optogenetic inhibition produced the opposite behavioral outcomes, enhancing depression-like behavior and reducing risk-seeking. Activation of SNr-VGaT inputs to the DR also promoted robust feeding behavior, even overcoming conditioned taste aversion. Although increasing GABA release in the DR did not enhance overall food motivation, suppressing GABA release from SNr terminals in Halo mice impaired the motivation to work for food rewards. Together, these findings identify an inhibitory SNr-to-DR circuit as a key regulator of emotional state, risk-related decision making, and feeding behavior, highlighting a previously unrecognized role for nigral GABAergic signaling in coordinating motivated behaviors.

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Poster

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Topic: H.03. Motivation

Support: NIH Intramural Research Program

Title: Regulation of median raphe GABAergic neurons and positive reinforcement in mice

Authors: *L. NICOLAS, Y. ARIMA, B. GETACHEW, Z. YE, S. IKEMOTO;
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Abstract: Understanding the substrates and circuits that underlie positive reinforcement and motivated behaviors is essential for revealing their potential roles in addiction. The median raphe region (MnR) plays a significant role in regulating motivated behaviors. Previous research has demonstrated that pharmacological inhibition of MnR neurons induces goal-directed and reinforcing behavioral effects. Despite these findings, the specific neuronal populations and afferent circuits responsible for these effects remain largely unknown. Moreover, there is limited information regarding the afferent inputs that modulate MnR neuron activity. The MnR neurons may be influenced by the lateral habenula (LHb), which provides extensive glutamatergic projections to the MnR. Given this relationship, the present study had two primary objectives: first, to identify the MnR neuronal populations involved in reinforcement; and second, to investigate whether LHb neurons regulate MnR activity. To pinpoint reinforcement-related MnR neuronal populations, an inhibitory opsin was expressed in a cell type-specific manner using Cre mouse lines. The study utilized optogenetic inhibition of MnR VGAT neurons, ePet neurons, and VGluT3 neurons. Notably, only the inhibition of MnR VGAT neurons was found to be reinforcing in an intracranial self-administration task, where mice learned to lever press to receive photoinhibition. To assess whether LHb afferents regulate this population, excitatory or inhibitory opsins were expressed in LHb neurons, and GCaMP was expressed in MnR VGAT neurons. Through optogenetic manipulation, activation of LHb-->MnR pathways increased the activity of MnR VGAT neurons, while inhibition of these pathways decreased their activity. In summary, the results indicate that MnR VGAT neurons are involved in reinforcement and positive affect. Furthermore, LHb afferents modulate the activity of this neuronal population, supporting the idea that the LHb bidirectionally regulates MnR GABAergic neurons in mice.

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Poster

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Support: NIH Grant R21MH129989
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Title: Dopamine modulation of prefrontal activity during ongoing reward-motivated behavior

Authors: *A. BENSON[1], W.-J. GAO[2];
[2]Neurobio. and Anat., [1]Drexel Univ., Philadelphia, PA

Abstract: Motivational deficits, including reduced goal-directed action, impaired effort allocation, and difficulty maintaining engagement with rewarding outcomes, are disabling

features of neuropsychiatric disorders such as schizophrenia, depression, and ADHD. These symptoms often resist current treatments, highlighting the need to identify neural mechanisms that regulate motivated behavior as it unfolds. Dopamine has long been implicated in reward processing, reinforcement, and effort-based behavior, while medial prefrontal cortex (mPFC) activity is linked to effort allocation, attentional control, and behavioral regulation. However, how dopamine release in the mPFC relates to local prefrontal neuronal activity during distinct phases of ongoing reward-motivated behavior remains unclear. To address this, we developed a reward-driven jump task in which food-restricted mice perform jumps of increasing difficulty, 10, 13, and 15 cm, to obtain a palatable reward. We used dual-color fiber photometry in the mPFC to monitor dopamine release with GRAB-DA3h and population-level calcium activity with jRGECO1a during reward-directed behavior in male and female mice. To distinguish action-related signals from reward-related signals, we separately aligned neural activity to jump onset, platform dismount, reward presentation, and reward consumption. Preliminary recordings show phasic prefrontal dopamine and calcium transients time-locked to motivated behavioral events. Dopamine signal rises before jump execution and remains elevated after the action, whereas calcium activity shows a brief increase followed by a decline, suggesting that prefrontal dopamine and calcium dynamics track distinct components of ongoing reward-directed behavior. Separating jump-related activity from reward presentation and consumption further suggests that mPFC dopamine is not simply a response to reward delivery but may modulate prefrontal activity during the organization and execution of motivated actions. Analyses will quantify event-aligned dopamine and calcium dynamics across jump heights and behavioral epochs, as well as the temporal relationship between dopamine and calcium peaks. All analyses will include sex as a biological variable. Together, these data support a model in which mesocortical dopamine dynamically modulates prefrontal neuronal activity during ongoing motivated behavior. *Supported by NIH/NIMH R21MH129989, R01MH131053, and PA CURE Grant SAP # 4100085747 to WJG.*

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Poster

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Topic: H.03. Motivation

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Title: Reciprocal connections between the thalamic paraventricular nucleus and ventral subiculum regulate dopamine in the nucleus accumbens shell

Authors: S. H. LI, S. LI, *G. J. KIROUAC;
Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Dysregulation of dopamine (DA) release in the nucleus accumbens shell (NAcSh) is implicated in drug addiction, depression and schizophrenia. Previous research has shown that stimulation of the anterior aspect of the thalamic paraventricular nucleus (aPVT) and ventral hippocampal subiculum (vSub) can evoke DA release in the NAcSh. The present study used intersectional viral tracing in rats to demonstrate that PVT-NAcSh and vSub-NAcSh projection neurons are interconnected and provide a dense converging innervation of the NAcSh. We also combined optogenetics and fiber photometry to determine if reciprocally connected aPVT- and vSub-NAcSh neurons work together to regulate DA in urethane anesthetized rats. An intersectional viral strategy was used to express the excitatory opsin Chrimson in aPVT- and vSub-NAcSh neurons in combination with DA biosensor dLight1.3b in the NAcSh. In other rats, the inhibitory opsin Jaws was expressed in DA neurons that project to the NAcSh. Three weeks later, fiber optic probes were implanted in the aPVT, vSub, and NAcSh. Optoactivation of Chrimson expressing aPVT or vSub soma regions or Chrimson expressing vSub/aPVT fibers in the reciprocally connected region evoked DA release in the NAcSh. In addition, optoinihibition of DA fibers in NAcSh prevented the DA evoked release from optoactivation of the soma regions of the aPVT- and vSub-NAcSh projecting neurons. The results of ongoing experiments that will determine if connections between the reciprocally connected region are recruited to evoke DA release from the aPVT and vSub will be presented at the meeting. This research describes a novel and tightly connected limbic circuit that regulates DA levels in a region of the striatum essential for mediating motivation and reward.

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Poster

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Topic: I.04. Executive Functions

Support: NIMH Intramural Research Program (IRP)

Title: A selective cell type projection from the islands of Calleja to the mediodorsal thalamus

Authors: *M. LOWRIE[1,4], A. BOURD[1], S. SHIRLEY[2], D. GARROD[2], S. BRADLEY[3], H. A. TEJEDA[2], K. MELETIS[4], Y. CHUDASAMA[1,3];
[1]Section on Behavioral Neurosci., [2]Unit on Neuromodulation and Synaptic Integration, [3]Rodent Behavioral Core, NIMH, Bethesda, MD; [4]Dept. of Neurosci., Karolinska Inst., Stockholm, Sweden

Abstract: The islands of Calleja (ICj) are interconnected clusters of GABAergic granule neurons and large spiny neurons located within the olfactory tubercle. Interposed between the septum, nucleus accumbens, ventral pallidum, and amygdala, the ICj is positioned to influence circuits regarding motivation, decision-making, and impulsivity. Owing to its dense expression of

dopamine receptor 3 (Drd3), ICj is a primary binding site for Drd3-targeting pharmacotherapies used to treat neuropsychiatric conditions presenting deficits in these areas. Since ICj is difficult to target in vivo, its connectivity, molecular composition, and effects on behavior remain poorly understood. Our goal is to map the organization, composition, and function of the ICj to understand its role in the circuitry of neuropsychiatric disorders and their treatments. We generated a Drd3-Cre knock-in rat line using CRISPR/Cas9 technology (LE-Drd3$^{em3(cre)Davis}$; RRRC #001027) to enable selective targeting of Drd3-expressing ICj neurons. We validated the Drd3-Cre line using behavioral phenotyping, fluorescent in situ hybridization, and immunohistochemistry. Analysis of Drd3-Cre expression across the brain revealed enriched labeling in the ICj, dorsal hippocampus, hypothalamus, and cortical layer 5. This genetic access allowed us to characterize ICj connectivity and molecular composition as a foundation for subsequent functional manipulations of ICj circuits during behavior. We next injected Cre-dependent AAV into the ICj of Drd3-Cre rats (n=4) revealing dense intra-ICj connectivity and projections to the mediodorsal thalamus (MD). Whole-cell recordings from MD neurons during optogenetic stimulation of ICj axons confirmed functional ICj input to MD. Retrograde tracing further demonstrated that MD-projecting ICj neurons are confined to the large-neuron population, suggesting that local interactions between GABAergic granule cells and large projection neurons regulate ICj output to MD. The MD participates in cognitive function through its interactions with the prefrontal cortex (PFC). We therefore examined inputs to these projection neurons and found direct PFC innervation of MD-projecting ICj neurons, supporting a PFC-ICj-MD circuit. We identified molecular markers distinguishing ICj projection neurons from granule cells via publicly available single-nucleus RNA-sequencing datasets. Immunohistochemistry combined with retrograde tracing validated markers for MD-projecting ICj neurons. These anatomical, molecular, and functional data provide a foundation for ongoing cell-type-specific manipulations to determine how ICj activity shapes cognitive behavior.

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Poster

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AKIVA Foundation
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Title: Striatal temporal interference stimulation modulates human motivation

Authors: *S. LOSACCO[1,2], P. VASSILIADIS[4], M. DI PONZIO[3], L. HO DAC[1], F. WINDEL[1], A. MARIN VARGAS[5], F. KARIMI[6], A. NUTI[1], V. DE SETA[7], E. NEUFELD[6], A. MATHIS[8], G. DEROSIERE[9], E. MORAUD[1], P. MACEIRA ELVIRA[10], M. HUSAIN[11], F. C. HUMMEL[12]; [1]École polytechnique fédérale de Lausanne (EPFL), Lausanne, Switzerland; [3]Neuro-X Inst., [2]Defitech Chair of Clin. Neuroengineering, Neuro-X Inst. (INX), Ecole Polytechnique Fédérale de Lausanne (EPFL), Geneva, Switzerland; [4]Max Planck Univ. Col. London Ctr. for Computat. Psychiatry and Ageing Res., Univ. Col. London, London, United Kingdom; [5]Brain Mind Institute, École Polytechnique Fédérale De Lausan, Geneve, ; [6]Fndn. for Res. on Information Technologies in Society, Zurich, Switzerland; [7].NeuroRestore, Swiss Federal Inst. of Technol. (EPFL), Lausanne Univ. Hosp. (CHUV) and Univ. of Lausanne (UNIL), Lausanne, Switzerland, Lausanne, ; [8]EPFL, Geneva, ; [9]Ctr. de Recherche en Neurosci. de Lyon, Bron, ; [10]Wyss Ctr. for Bio and Neuroengineering, Sion, ; [11]Univ. of Oxford, Oxford, ; [12]Defitech Chair of Clin. Neuroengineering, BMI and CNP, Swiss Federal Inst. of Technol. (EPFL), Genève, Switzerland

Abstract: Motivation is a fundamental aspect of human behavior, requiring the evaluation of whether prospective rewards justify the effort they entail - a process disrupted in patients suffering from apathy and associated with striatal circuits. Motivation deficits are widespread, impacting several neurological and psychiatric conditions and determining poor quality of life. Previous research has highlighted the key role of the striatum in cost-benefit decision-making in humans (Schmidt *et al.*, 2008). However, due to its deep localization within the brain, focal stimulation of the striatum in humans has so far not been possible non-invasively, therefore its causal contribution remains unclear. Here, we leveraged a new non-invasive brain stimulation technology, transcranial temporal interference stimulation (tTIS), to target the striatum (Vassiliadis *et al.*, 2024 Nat Hum Beh; Wessel, Beanato *et al.*, 2023 Nat Neurosci; Vassiliadis, Beanato *et al.*, 2026 Nat BME). In this randomized, double-blinded, cross-over study, we applied either facilitatory or inhibitory tTIS, respectively intermittent (iTBS) or continuous theta-bursts (cTBS) stimulation, or an active high-frequency control (HF) to the striatum. Twenty-four healthy participants performed an effort-based decision-making task, requiring them to trade monetary rewards for physical efforts, before, during and after tTIS, with concurrent pupillometry. This task provides the opportunity to dissect the computational mechanisms underlying motivated behavior and the effects of striatal tTIS. Facilitatory iTBS-tTIS accelerated decisions, increased effort production, and amplified early pupillary responses during choice, whereas inhibitory cTBS-tTIS slowed decisions and reduced post-decision pupil dilation. Drift-diffusion modeling revealed that iTBS-tTIS biased decisions towards accepting effort and increased evidence accumulation rates. Invasive recordings in a patient with Parkinson's disease further showed reduced peri-decisional theta activity in the subthalamic nucleus during iTBS-tTIS related to decision making processes (Cavanagh & Frank, 2014, Trends Cogn. Sci.). Within this framework, the iTBS-tTIS-induced reduction of STN theta parallels the behavioral shortening of response times and the increase in drift rate and decision bias observed in the healthy cohort, suggesting a modulation of the decision process that promotes engagement in effort. Overall, these findings demonstrate that striatal tTIS can bias basal ganglia circuits during effort-based decision-making.

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Poster

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Topic: H.03. Motivation

Support: HHMI

Title: Reward-responsive cholinergic interneurons in dorsal striatum

Authors: *D. ZHANG[1], A. BEYENE[2];
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Abstract: Cholinergic interneurons (ChIs) in the striatum play important roles in modulating striatal circuit activity and dopaminergic signaling. Although ChIs constitute only ~1-2% of striatal neurons, they are sparsely distributed throughout the striatum and exert widespread influence on striatal function. Previous studies have typically relied on recording methods that sample ChIs from limited regions of the striatum or at the single-neuron level. Consequently, how ChIs dynamically encode information across the dorsolateral (DLS) and dorsomedial (DMS) striatum at the population level remains poorly understood.Here, we used large-scale longitudinal two-photon calcium imaging to record the activity of hundreds of ChIs across both DLS and DMS in behaving mice, enabling simultaneous monitoring of ChI populations at single-cell resolution. We found that ChIs exhibited highly heterogeneous activity patterns, including tonic activity and modulations associated with ongoing movements. These activity patterns varied substantially across neurons, revealing a diverse repertoire of cholinergic dynamics distributed throughout the dorsal striatum.Together, these findings provide a population-level view of ChI activity across the dorsal striatum and reveal substantial functional heterogeneity within the striatal cholinergic network. These results suggest that ChIs encode diverse aspects of behavioral state and movement across both DLS and DMS, highlighting previously unappreciated complexity in cholinergic signaling throughout the dorsal striatum.

Disclosures: D. Zhang: None. **A. Beyene:** None.

Poster

PSTR107: Neural Circuits for Reward, Value, and Motivated Behavior

Location: WCC Halls A-C

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Title: Phasic dopamine signals associated with behavioral performance over prolonged timescales in monkeys

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Abstract: Slowly varying internal states govern our ability to sustain goal-directed behavior over minutes to hours, imposing fundamental constraints on cognitive performance, yet the neural signals that track these states remain poorly defined. Dopamine is a powerful modulator of motivated behavior, but its best characterized signals are in the form of reward prediction errors (RPEs) that are typically observed at seconds timescales. Whether these phasic signals also carry information about slower, ongoing states of behavioral performance has not been directly tested. Here, we recorded subsecond dopamine concentration changes across multiple sites in the caudate nucleus and putamen of rhesus monkeys performing a reward-guided saccade task. Task performance oscillated over tens to hundreds of trials, demonstrating fluctuating internal states of sustained engagement. We found that single-trial dopamine signals were strongly modulated by these slowly evolving performance states, in a manner dissociable from trial-level RPE and cumulative reward rate. This relationship was biased toward future rather than past performance windows, indicating that dopamine tracks motivational state prospectively rather than simply reflecting the reward history, on which prediction errors are computed. Furthermore, performance-state modulation was concentrated in the caudate nucleus rather than the putamen, consistent with the distinct roles of these regions in oculomotor and skeletomotor control and suggesting that state-dependent dopamine signals are organized according to the behavioral demands of the task. These findings demonstrate that phasic dopamine signals in the dorsal striatum simultaneously reflect fast learning signals and slowly evolving internal states, linking dopamine's canonical RPE function to its broader role in sustaining motivated performance.

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Poster

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R01MH134845

Title: Orbitofrontal cortex microstimulation reveals state-dependent modulation of expectation updates

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Abstract: Efficient guidance of motivated behavior requires the constant generation and updating of expectations about dynamic environments. Maintaining incorrect expectations in the face of new information hinders contextually appropriate behaviors—a core feature across many neuropsychiatric conditions. Here, we sought to determine the contributions of one brain region often implicated in the generation of affective expectations—the orbitofrontal cortex (OFC)—to expectation updating. We trained rhesus macaques on a task that allows for quantification of expectation-guided behavior. Monkeys were trained to associate different pictures with fluid rewards of varying putative pleasantness (sweet concentrations of sucrose and bitter concentrations of quinine). On each trial, one (forced choice trials) or two (choice trials) pictures were presented, and monkeys made selections by fixating the image and releasing a touch-sensitive bar. Selections triggered a reward bolus followed by a 4 second instrumental response period in which repeated taps of the bar produced additional small amounts of the same reward. During testing sessions, a subset of trials resulted in the delivery of a reward which differed from the monkey's expectation. Likewise, electrical microstimulation was delivered to OFC via acutely implanted platinum-iridium electrodes on a subset of trials. In comparing instrumental response updating during mismatch trials with and without stimulation, we found that stimulation effects were consistent with a modulation of expectation strength. In some sessions, OFC stimulation disrupted expectations, facilitating faster updating to prediction errors. In others, OFC stimulation enhanced expectations, causing slower updating to prediction errors. Heterogeneity in effects could not be attributed to differences in anatomical stimulation targets. However, some heterogeneity was explained by the monkey's internal state, inferred through behavioral readouts including reaction time and pupil diameter. To characterize the neural underpinnings of these state-dependent effects, neurophysiological recordings are ongoing. This pattern of results supports the idea that OFC is causally involved in expectations and expectation updating and that baseline physiological states interact with stimulation to produce differential effects.

Disclosures: J.A. Charbonneau: None. **E.L. Rich:** None.

Poster

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Title: Neural dynamics of updating taste reward expectations

Authors: *S. MCCONNELL[1], E. L. RICH[2];
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Abstract: Expectations of reward play a critical role in cognition and decision-making, allowing us to predict the outcomes of certain actions, and influencing which actions we take. Expectations also inform how we interpret sensory input. However, when our expectations are wrong, the ability to flexibly shift our behavior in response to unanticipated circumstances is critical for our well-being. For example, recognizing that the milk in the fridge that you thought was still good has actually spoiled protects you from an unfortunate episode of food poisoning. In order to better understand the neural dynamics involved in these processes, I recorded neurons from the gustatory cortex, as well as orbitofrontal cortex areas 11 and 13, while monkeys performed a task in which different image cues predicted the taste of a fluid outcome (from sweet to bitter). Each trial could be either forced-choice (where only one image was presented for selection) or free-choice (where a choice between two images was presented). In order to select an image, the monkey was required to fixate the image and release a touch-sensitive bar, which was followed by an initial bolus of fluid. Following image selection, there was a four-second period during which the monkey could tap the touch-sensitive bar to receive additional small deliveries of the same fluid. Monkeys consistently chose sweeter options, and tapped more for them. Once associations were established, a small percentage of trials became “mismatch” trials, in which the fluid delivered did not match the cue image. On these trials, tapping behavior initially reflected the expected outcome, but shifted over the four-second window in accordance with the actual fluid received. Simultaneous recordings from the orbitofrontal cortex and the gustatory cortex were acquired in two monkeys. Preliminary analysis suggests that both the GC and the OFC have information about expected and received outcomes, which updates over the course of mismatch trials.

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Poster

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Program #/Poster #: PSTR107.18/FF23

Topic: H.03. Motivation

Support: R01MH134845

Title: Value- and gaze-independent encoding of perceptual difficulty in orbitofrontal cortex

Authors: *C. L. RODRIGUEZ DELIZ[1], E. L. RICH[2];
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Abstract: Multi-attribute decisions require comparing options across stimulus dimensions, a process that varies in difficulty depending on how attribute information is represented (Perkins, Gillis & Rich, 2024; Perkins & Rich, 2025). When the mapping between a visual cue and its value differs across like attributes, direct comparison requires an additional mental inversion step, introducing measurable inefficiencies into choice behavior. Here we ask whether this perceptual difficulty is represented in the prefrontal cortex, and if so, whether it is encoded independently of value and gaze. Using single-unit electrophysiology in two rhesus macaques performing a multi-attribute decision-making task, we find that a subpopulation of neurons in orbitofrontal cortex (OFC) encodes a parametric difficulty signal that scales with mapping inconsistency across like attributes. This signal is present in OFC but absent in frontal eye fields (FEF). Difficulty-encoding neurons do not jointly encode value variables above chance, suggesting that difficulty and value are carried by functionally distinct neural subpopulations within OFC. Moreover, this difficulty signal persists after accounting for gaze-dependent comparison processes, indicating that it reflects a static, gaze-independent feature of the choice environment rather than a dynamic consequence of attribute sampling. Our results reveal a dissociation within OFC between gaze-dependent value comparison mechanisms and gaze-independent representations of decision difficulty, with implications for understanding how prefrontal circuits support cognitive effort allocation during decision making.

Disclosures: C.L. Rodriguez Deliz: None. **E.L. Rich:** None.

Poster

PSTR108: Executive Function in Humans

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Topic: I.04. Executive Functions

Support: NIH Grant U01NS117839
Center for Neural Science and Medicine Postdoctoral Fellowship

Title: Stimulus-specific recruitment of human amygdala neurons predicts episodic memory encoding success

Authors: *J. XIAO[1], J. DAUME[1], Y. SALIMPOUR[2], N. KURILENKO[1], C. P. MOSHER[1], W. S. ANDERSON[3], T. VALIANTE[4], A. MAMELAK[1], U. RUTISHAUSER[1];

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Abstract: Our daily experiences are filled with a constant flow of sensory information, yet only a small subset is encoded into long-lasting episodic memory. The neural mechanisms that determine which events are preserved in memory and which are forgotten remain poorly understood. Using intracranial recordings from 42 neurosurgical patients (49 sessions, 1871 neurons), we examined single-neuron activity and local field potentials in the human brain during memory encoding and retrieval. Participants viewed novel visual stimuli from five categories and later performed recognition with confidence ratings. We first identified category-selective neurons by testing for different responses across stimulus categories (1×5 ANOVA). Category neurons were observed above chance levels in four regions: ventral temporal cortex (VTC), amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC). In the amygdala, category-selective neurons showed enhanced firing during encoding for items that were subsequently remembered compared to those later forgotten. This difference was observed in the amygdala at around 350 ms after stimulus onset, preceding a weaker hippocampal effect at approximately 1300 ms. Cells in the VTC and vmPFC, while strongly category selective, did not predict memory encoding success, highlighting the specificity of this effect to the amygdala. Critically, amygdala firing rates tracked memory strength in a graded manner, with highest activity for high-confidence remembered items, intermediate responses for low-confidence remembered items, and lowest responses for forgotten items. These results indicate that amygdala category neurons encode not only whether an item will be remembered, but also the strength of the resulting memory. One potential mechanism linking stronger category-cell responses to enhanced memory formation is increased coordination with ongoing network oscillations. Consistent with this, spike-field coherence within the amygdala was significantly stronger for subsequently remembered than forgotten items. We next assessed inter-regional coordination between the amygdala and hippocampus and found that successful memory formation was accompanied by enhanced spike-field coherence between the activity of category cells in the amygdala and hippocampal field potentials, indicating stronger amygdala-hippocampal coupling. Together, our findings demonstrate that recruitment of stimulus-specific representations in the amygdala predicts episodic memory formation. This data suggests that category cells in the amygdala may be a potential target for interventions to treat disorders affecting episodic memory.

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Poster

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Topic: I.04. Executive Functions

Support: NSF Grant BCS-2219800

Title: A shared neuronal substrate for internal performance monitoring and external feedback processing in human medial frontal cortex

Authors: *J. GAVENAS, C. REED, J. CHUNG, D. BONDA, A. MAMELAK, U. RUTISHAUSER;
Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Humans can detect errors through both internal self-monitoring and external feedback, and both types of errors drive behavioral adjustments and learning. EEG and fMRI investigations of internal and external error signals (e.g. the error-related negativity and feedback-related negativity) have suggested they might share a common neuronal substrate within human medial frontal cortex (MFC), but whether the mechanisms by which these two types of error are processed are identical remains unclear. We recorded activity from 401 MFC neurons (259 preSMA, 142 dACC) while human epilepsy patients (N=13, 16 sessions) performed two cognitive tasks: (1) a Stop-Change task in which participants could only determine whether they executed a required response change through internal self-monitoring (no feedback given), and (2) a Reversal Learning task with probabilistic feedback and unpredictable contingency swaps such that errors could only be detected following feedback. We identified 146 neurons (36.4%) whose activity encoded self-monitored errors following response in the Stop-Change task and 89 neurons (22.2%) that encoded choice outcome following feedback in the Reversal Learning task. 37 neurons (9.2%) encoded both error types ($p<0.001$, binomial test). These context-invariant error neurons define a common neuronal substrate for internal and external error processing within human MFC. At the population level, decoders trained to decode errors given activity 0.5-1.0s post-response (Stop-Change) or feedback (Reversal Learning) exhibited significant cross-task generalization ($p<0.05$, permutation test), whereas decoders trained on earlier activity did not generalize across tasks ($p>0.05$) even though errors were decodable within each task context at those times ($p<0.05$ for both tasks). These findings suggest that internal and external errors initially engage distinct computations before converging on a shared context-invariant error representation in MFC, consistent with a hierarchical organization of performance monitoring processes.

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Poster

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Topic: I.04. Executive Functions

Support: NIH Grant U01NS117839
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Title: Neural coding of complex behavior in humans: from widespread engagement to microtask tuning

Authors: ***Y. JIN**[1], L. LI[1], J. CHUNG[2], C. REED[2], D. BONDA[2], A. MAMELAK[2], U. RUTISHAUSER[2,1], M. MEISTER[1];
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Abstract: Complex human behavior, such as driving a car, involves flexible sequencing of many brief tasks in order to achieve a goal. Much previous research has studied isolated tasks; however, how the brain combines these "microtasks", controls their sequence, and integrates them into longer goal-directed behaviors remains unknown. Here, we report single-neuron recordings from human subjects engaged in a naturalistic, goal-directed behavior: driving a simulated car around a virtual race track, while switching between interleaved microtasks such as managing speed and tracking fuel. We isolated 1,077 neurons across 10 patients over 19 sessions, with synchronized eye tracking and joystick control. We found that across 7 brain areas, 71% of neurons are modulated by this activity, with subsets tuned to many distinct microtasks and track locations, from fixation onsets to gas station entrances. Neural engagement scales inversely with driving performance ($r = -0.57$), suggesting more efficient coding as performance improves. Neural dynamics span from sub-second bursts to minute-long ramps, and their peak latencies vary across brain regions. Clustering of tuning profiles reveals response types shared across subjects, and a population decoder reconstructs the car's track position using only a subset of neurons. In conclusion, a complex behavior like driving engages widely distributed neural populations with interpretable, structured activity across multiple timescales. These observations pave the way for human single-neuron recording to test specific circuit models for how the brain controls goal-directed behaviors.

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Poster

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Program #/Poster #: PSTR108.04/FF27

Topic: I.04. Executive Functions

Title: Computational modeling shows that visual category tuning supports one-shot learning in human medial temporal lobe

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Abstract: The medial temporal lobe (MTL) is critical for rapid learning, but the underlying mechanisms remain little understood. Human single-neuron recordings during visual recognition tasks have identified distinct neurons that encode either visual categories or stimulus familiarity, but not both. Why these two response types coexist remains unclear. We used and enhanced a computational model of familiarity recognition to test whether category structure emerges as a consequence of organizing representations to optimize rapid episodic memory formation. To test this hypothesis, we used the HebbFF model (Tyulmankov et al. 2022, Neuron), a feedforward neural network with Hebbian synaptic plasticity capable of single-trial learning. We trained the network on natural image embeddings on a familiarity recognition task. Applying random rotations, crops, flips, and contrast adjustments as augmentations to the training dataset improved familiarity recognition performance at longer delays and produced hidden unit response properties that more closely matched those seen in the human single-neuron recordings. In particular, such models reproduced a bimodal distribution of novelty and familiarity selectivity similar to that observed in MS neurons (which encode stimulus familiarity), whereas models trained without image augmentations did not. Decoder analyses further showed that model hidden units exhibited saturation properties comparable to those seen in neural populations. Finally, while it was difficult to disentangle the initial category representation in the image embeddings with those emerging in the hidden layers, we found that familiarity recognition performance was strongly correlated with the ability of the hidden units of the model to encode visual categories across models. Together, these results suggest that category structure can emerge naturally when optimizing for one-shot learning, especially when each episode can generate slightly different visual scenes. This provides a potential explanation for the coexistence of visually selective category and memory-selective familiarity neurons in the MTL and supports the idea that visual representations are shaped by the computational demands of rapid episodic memory.

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Poster

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Topic: I.04. Executive Functions

Support: NFRF - Brains in the Wild project

Title: Time cells in the human brain during working memory maintenance

Authors: *X. XIAO[1], T. A. VALIANTE[2], U. RUTISHAUSER[3], J. TAXIDIS[4];
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Abstract: Working memory, the active retention of information over short periods, is a fundamental cognitive function, yet its underlying neural mechanisms in humans remain poorly understood. Recent rodent studies have revealed sequences of “time cells”, i.e. neurons spiking one after another after the presentation of a memory cue, that encode both the cue identity and the time since its presentation. This temporal coding offers an alternative mechanism for maintaining working memory, beyond more classical models of persistent spiking. Whether similar temporal coding exists in the human brain, however, has not been established.To investigate this, we analyzed single-neuron recordings from three publicly available working memory datasets collected from neurosurgical patients implanted with intracortical electrodes. Two datasets contained neurons from the medial frontal and medial temporal lobes of patients performing similar visual working memory tasks (Kyzar et al., 2024; Daume et al., 2024), and one dataset contained medial temporal lobe neurons from patients performing a verbal working memory task (Boran et al., 2020). We found time cells with temporally tuned activation during working memory maintenance, collectively forming robust sequences that tiled a delay period. Time-cell coordination in the hippocampus reflected successful memory maintenance whereas in the pre-supplementary motor area it reflected memory load. Moreover, we identified time cells that spiked selectively after the presentation of individual memoranda, supporting an alternative mechanism for maintaining cue information during working memory to that from persistent spiking.Together, these findings demonstrate that temporally specific firing in medial frontal and temporal regions supports human working memory, highlighting the integrative role of temporal coding in cognition.

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Poster

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Topic: I.04. Executive Functions

Title: Accelerating human single-unit neuroscience using high-density 128-channel stainless steel microelectrode arrays: mapping the subthalamic nucleus during response inhibition

Authors: *H. COURELLIS[1,2], M. YEBRA[4], J. GAVENAS[5], S. CHENG[6], C. P. MOSHER[6], J. ZHU[2], F. WU[8], M. TAGLIATI[3], A. MAMELAK[2], U. RUTISHAUSER[7,9];
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Abstract: The advent of high-density silicon microelectrodes in the field of human single-unit neurophysiology has expanded our ability to map the cortical surface during neurosurgical

procedures. However, despite both clinical and scientific interest in performing such recordings deeper in the brain, the required length and risk of electrode fracture make such deeper recordings impossible with current technology. Thus, microelectrode recordings in the basal ganglia during Deep-Brain Stimulation (DBS) surgery are, to this day, performed one depth at a time using a small number of single channel microelectrodes. Here, we demonstrate that large-scale, high-density extracellular recordings are achievable in the human basal ganglia using a novel 128-channel microelectrode array fabricated on a stainless-steel substrate, thus obviating the risk of electrode fracture and allowing for the development of very long electrodes that can reach the human basal ganglia. Microelectrodes on this array are spread over 3.175mm with a vertical pitch of 50μm and horizontal pitch of 43.3μm, allowing for dense recording of local field potentials and observation of the same action potential waveform across multiple channels. We use this information to perform robust spike sorting using state of the art motion-artifact correction and spike sorting techniques. Using this microelectrode array, we reliably perform simultaneous recording from ~100 neurons in the subthalamic nucleus (STN) of PD patients undergoing DBS surgery. We perform these recordings during resting wakefulness and characterize neuronal β-oscillatory dynamics as well as neuronal entrainment and waveform modulation throughout the cardiac cycle. Furthermore, we perform recordings while patients are engaged in a Stop Signal task and demonstrate that core findings from previous work, which required pooling data across many subjects, can be recapitulated in individual patients. Furthermore, we show that the geometry of encoded task variables can be studied with single-session and single-trial resolution. Indeed, the number of neurons required to match state-of-the-art publications, whose data were collected over the course of several years, can be attained in a single recording session with our approach. Our work heralds the beginning of a significant acceleration in the science dedicated to the mapping of deep structures within the human brain, and provides a novel approach through which our understanding and treatment of neurological disease can be revolutionized.

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Poster

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Topic: I.04. Executive Functions

Support: U01NS117839

Title: Neural representations of confidence in the human medial temporal lobe and medial frontal cortex are largely domain-specific across memory and perceptual decisions

Authors: *E. LAYHER[1], M. B. MILLER[3], A. N. MAMELAK[1], C. M. REED[1], U. RUTISHAUSER[2];
[2]Dept. of Neurosurgery, AHSP #6432, [1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [3]Univ. of California, Santa Barbara, CA

Abstract: Confidence ratings are commonly used as a behavioral index of one's subjective sense of certainty in a decision (known as metacognition). However, the degree to which the neural substrates of metacognition are shared across cognitive domains or specialized for specific tasks remains actively debated. To assess the degree to which metacognition is neurally represented in a domain-general versus domain-specific manner, we developed a novel paradigm combining recognition memory and visual discrimination tasks, tightly matched in structure and difficulty. Participants first studied a series of images, each embedded with 100 randomly placed red or blue dots. At test, each image was presented for 1 s and participants made either a recognition judgment (old/new) or a dot discrimination judgment (more red or blue), each accompanied by a simultaneous high/low confidence rating. Epilepsy patients undergoing intracranial seizure monitoring (15 sessions, 11 subjects) performed the task while single-unit activity was recorded bilaterally via Behnke-Fried depth electrodes from the amygdala and hippocampus (collectively, medial temporal lobe; MTL) and dorsal anterior cingulate cortex and pre-supplementary motor area (collectively, medial frontal cortex; MFC). To identify confidence-selective neurons, we compared firing rates between high and low confidence trials during stimulus presentation ($p < .025$ in either task). Confidence-selective neurons were identified in 21/270 (7.8%) MTL and 26/214 (12.1%) MFC neurons. In the MTL, only 1/21 (4.8%; χ^2 n.s.) confidence-selective neurons showed selectivity across both tasks, indicating domain-specific confidence coding. In the MFC, 4/26 (15.4%; χ^2 $p < .05$) neurons were confidence-selective across both tasks, suggesting possible domain-general contributions in a subset of neurons, though confidence coding remained largely domain-specific. For comparison, visually-selective neurons that are defined by preferential firing to specific image categories were identified in 87/270 (32.2%) MTL neurons, of which 43/87 (49.4%) maintained selectivity across both tasks despite category being task-irrelevant during visual discrimination. Together, these findings suggest that metacognitive confidence signals are predominantly domain-specific at the single-unit level in the human MTL and MFC, though ongoing data collection will clarify whether a subset of MFC neurons represent confidence in a domain-general manner.

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Support: BBSRC DPhil Student Scholarship, awarded to Julia Dabrowska.

Title: What are the EEG network dynamics supporting executive functioning during a task switching paradigm?

Authors: *J. K. DABROWSKA, S. SHATEK, B. GRIMES, M. VAN ES, M. WOOLRICH, G. SCERIF;
Univ. of Oxford, Oxford, United Kingdom

Abstract: Differences in executive function (EF) are linked to differential brain network composition and dynamic reconfigurations, yet particular network dynamics in this interplay remain unclear. Here, we apply dynamic network analysis to an adapted version of the Dimensional Change Card Sort (DCCS) task - requiring sorting icons by shape or colour on a trial-by-trial basis, with the rule either repeating or switching between trials, and icons being congruent or incongruent with template images. Behavioural data and 64-channel saline EEG were collected from 45 adults using a mixed-block paradigm. The analytical pipeline uses Hidden Markov Model (HMM) methods to identify network dynamics of oscillatory activity at task and rest. Specifically, the HMM describes M/EEG time series as an underlying sequence of 'hidden' transient states, closely corresponding to canonical fMRI resting state networks. This enables prediction of network activation during specific tasks or periods, and subsequent estimation of state-specific power & coherence spectra, an array of summary statistics, and evoked potential analyses. The current analysis builds on a pilot study using these methods on 32-channel EEG, which established networks during a novel learning task, group differences of attentional demand, and a preliminary relationship between network characteristics and task performance. Here, our analysis focuses on comparing identified networks across trial type and congruency, and on their association with participant performance. Behavioural differences were significant in reaction time and accuracy, both for the traditional contrast of repeat and switch, and for congruency (repeat/switch: $p<0.0004$, $p<0.05$; two-way: $p<0.00001$). We note two participant subgroups: one with greater congruency costs, and the other more affected by switch costs. Preliminary network analyses indicate differences in frontal networks between lower- and higher-demand conditions, alongside a predictive relationship with task performance. Furthermore, we hypothesise differences in network dynamics between the two subgroups. This work extends our understanding of network mechanisms supporting flexible behaviour under competing task demands and is crucial for validating HHM-based methodological efficacy, enabling more cost-effective procedures to investigate network dynamics. Future work will extend to a DCCS variant incorporating rule reversal, in comparison to a naturalistic multitasking paradigm. Besides uncovering cognitive mechanisms, such findings can be beneficial for further understanding conditions involving impairments of cognitive flexibility and EF.

Disclosures: J.K. Dabrowska: None. **S. Shatek:** None. **B. Grimes:** None. **M. van Es:** None. **M. Woolrich:** None. **G. Scerif:** None.

Poster

PSTR108: Executive Function in Humans

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.09/FF32

Topic: I.04. Executive Functions

Title: The polar region of anterior insula leads anterior cingulate cortex during human target detection

Authors: *G. CHEN[1], W. HUANG[1], J. QUABS[1], J. PARVIZI[2];
[1]Stanford Univ., Stanford, CA; [2]Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Detecting behaviorally relevant events in a continuous stream of sensory input requires rapid coordination between sensory evidence, attentional control, and action selection. Although the anterior insula and anterior cingulate cortex (ACC), core nodes of the salience/action-mode network, are widely implicated in salience processing and cognitive control, it remains unclear how these regions coordinate in time to support successful target detection. Here, we used human intracranial EEG recordings during the Gradual-onset Continuous Performance Task (GradCPT) to resolve the millisecond-scale dynamics of insula-cingulate coordination. Among 51 patients with focal epilepsy, we identified significant target-related high-frequency broadband (HFB; 70-170 Hz) activity in both insula and ACC. Within the insula, responsive sites were concentrated in the polar region of anterior insula (INS; 56 sites), whereas 26 responsive sites were identified in ACC. Among INS sites, target responses were stronger and earlier toward more anterior and dorsal sites, suggesting an anatomically organized spatiotemporal architecture for target detection. In 5 participants with simultaneous responsive INS and ACC sites, ROL analysis revealed that INS responses preceded ACC responses during successful target detection (30 pairs, mean lead = 26 ms, $t_{29} = 2.77$, $p = 0.010$). This functional temporal precedence was supported by intrinsic effective connectivity, as cortico-cortical evoked potential analysis revealed stronger INS→ACC than ACC→INS connectivity ($t_{22} = 2.50$, $p = 0.020$), and the INS→ACC directionality index significantly correlated with the task-related INS lead ($r = 0.57$, $p = 0.005$). Finally, we examined how this temporal hierarchy changed during behavioral failure. During errors, INS and ACC responses were delayed yet enhanced relative to correct target detection, while only ROLs in INS sites reliably predicted trial outcome (correct vs. incorrect; mean accuracy: 69.0% ± 2.0%, $p < 0.05$). Critically, the INS lead over ACC was abolished during errors ($p = 0.792$), indicating that behavioral failure is associated with disrupted temporal coordination. Together, these findings identify the polar region of anterior insula as an early hub in human target detection, revealing a millisecond-scale INS-to-ACC temporal hierarchy that is supported by intrinsic effective connectivity and disrupted during behavioral failure.

Disclosures: G. Chen: None. **W. Huang:** None. **J. Quabs:** None. **J. Parvizi:** None.

Poster

PSTR108: Executive Function in Humans

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.10/GG1

Topic: I.04. Executive Functions

Support: Fulbright Morocco

Title: Enhanced Attention for Musicians Compared to Non-Musicians on Cued Visual Stroop

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Abstract: Music training is associated with enhanced executive functions, attentional control, and conflict monitoring, potentially reflecting neuroplastic adaptations in cognitive control networks(Zuk et al., 2014; Saarikivi et al., 2023). We examined whether musicians demonstrate altered neural responses to cognitive conflict during a visual Stroop task using event-related potentials (ERPs).Neurophysiological data were collected from young adults (N=49), including 23 musicians and 26 non-musicians. Mean ERP amplitudes were analyzed to assess P3a activity, occurring approximately 250-350 ms post stimulus window and reflecting attentional orienting processes (Polich, 2007). Visualization of spatial activation patterns associated with group and condition differences. Statistical analyses revealed significant effects of stimulus congruency at frontal and central electrode sites, including Fz ($F(1,51) = 4.79$, $p = .03$) and C2 ($F(1,51) = 4.47$, $p = .04$), indicating significantly larger amplitude for musicians relative to non-musicians. No significant interaction was found for incongruent conditions. Topographic distributions showed stronger frontal-central activation, suggesting enhanced attentional resource allocation during conflict processing.These findings suggest that long-term musical training may strengthen neural mechanisms involved in executive control and conflict monitoring even during visual tasks. Enhanced P3a responses in musicians support the hypothesis that musical experience contributes to more efficient attentional processing during cognitively demanding tasks.

Disclosures: N. Perla: None. **M. Lamouine:** None. **J.A. Bugos:** None.

Poster

PSTR108: Executive Function in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR108.11/GG2

Topic: I.04. Executive Functions

Support: Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan Grant No. BR27198099

Title: ERP STUDY OF THE BRAIN ACTIVITY DURING ATTENTION NETWORK TEST (ANT) PERFORMANCE IN CHILDREN

Authors: *D. MENGDIBAY[1], A. KAZAKBAYEVA[2,1], A. A. NURMANBETOVA[2], G. BORBASSOVA[2], M. MELNIKOV[1], M. ZHOLDASSOVA[1], A. KUSTUBAYEVA[1,2];
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Abstract: The attention development unfolds across the childhood along with brain maturation. While role of P300 in attention is well established, its earlier counterpart, N200 remains underinvestigated. The current study aims to investigate executive control-related N200 during the Attention Network Test (ANT) performance in healthy children and adolescents. Sixty-three healthy volunteers participated (30 females, age M=15.23, SD=4.91; 33 males, age M=14.28, SD=3.71; 2), divided into 5 age groups. The EEG was recorded using ANT-Neuro amplifier with 64 Ag/AgCl electrode system during the ANT task performance. The preprocessing included downsampling to 512 Hz, filtering 0.3-40 Hz, bad channel interpolation, ICA-based cleaning, and re-reference to linked mastoids. N200 amplitudes to target stimuli were averaged within central, anterior, and posterior networks. Network * Group interaction effect was observed (F=2.99; p=0,005), with N200 amplitude decreasing with age. Network * Sex interaction effect was also revealed (F=3.48; p=0.03). Specifically, N200 amplitude was more negative in males, compared to females. No main effect of the Group was identified. The reaction times (RT) suggest higher efficiency of executive control in older participants (F=2.66; p=0.043). Larger negative N200 amplitudes were found in males, possibly suggesting more effort to suppress automatic responses To add, smaller N200 amplitudes were revealed in older participants putatively evidencing the prefrontal cortex functional development.

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Poster

PSTR108: Executive Function in Humans

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.12/GG3

Topic: I.04. Executive Functions

Title: Who's in Charge? Neural Signatures of Agency When AI Takes Over Stages of Goal-Directed Action

Authors: *R. MOHAMMADSADEGH[1], Y. KWAK[2];
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Abstract: As artificial intelligence (AI) increasingly participates in human decisions, it remains unclear how the brain represents agency when different stages of goal directed behavior are transferred to AI. We designed a two stage task separating information sampling from final execution. Across within-subject conditions, AI sampled, placed, controlled both stages (Full AI), or was absent (No AI). Participants sampled information to locate a hidden target by clicking screen locations. Each click reduced available reward. Based on the sampled information, participants submitted their final response. We recorded neural activity from 19 participants during task performance using a 64-channel EEG and collected trial-by-trial ratings of sense of agency (SOA). SOA was highest in No AI (5.90±1.11), remained high when AI placed (AI Placer: 5.29±1.13), dropped sharply when AI sampled (AI Sampler: 3.12±1.20), and

was lowest under Full AI (2.22±1.41). We examined mediofrontal theta (4-8 Hz), as a marker of cognitive control and prediction-error signaling, and centroparietal alpha (8-14 Hz), linked to attentional gating and top-down suppression of task processing. During sampling, mediofrontal theta was reduced in AI Sampler and Full AI relative to No AI ($p<.001$). AI Placer did not differ, indicating that mediofrontal theta tracks who gathers information, rather than AI involvement generally. During placing, centroparietal alpha increased selectively in AI Placer ($p<.001$), with no comparable increase in other conditions. Reward and click count did not predict placing power, ruling out reward value and sampling effort as confounds. Centroparietal alpha during placing predicted trial-level SOA ($p<.001$), and the relationship was modulated by condition (interaction $p<.001$). Sampling power did not independently predict SOA once condition was controlled. These findings show that transferring sampling to AI reduces agency more strongly than transferring final execution, reflected in reduced mediofrontal cognitive-control signaling during AI-controlled sampling and condition-dependent centroparietal alpha during placing that tracks subjective control. These dissociable neural signatures may provide markers for monitoring and calibrating human agency in AI-assisted decision-making.

Disclosures: R. Mohammadsadegh: None. **Y. Kwak:** None.

Poster

PSTR108: Executive Function in Humans

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR108.13/GG4

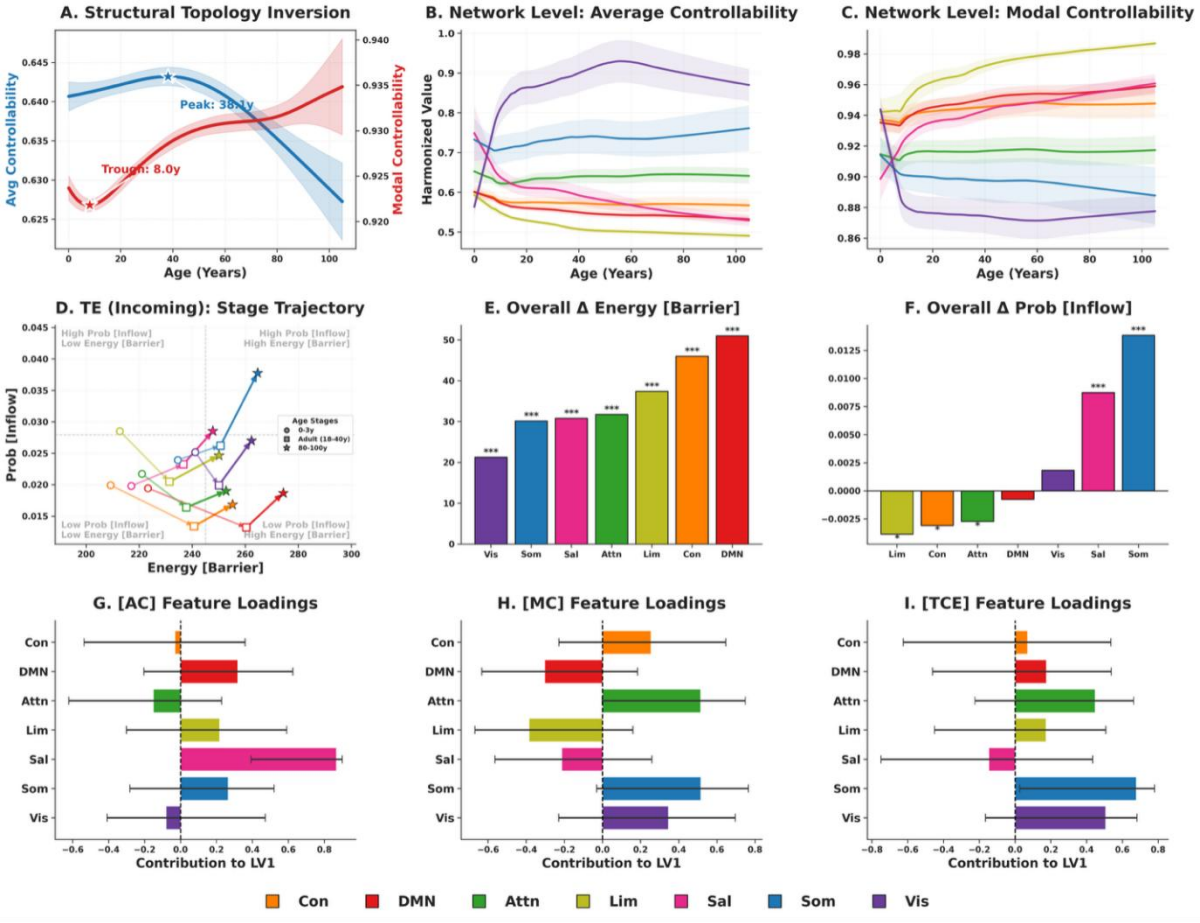
Topic: I.04. Executive Functions

Title: Brain energetic landscape and its associations with cognition across lifespan

Authors: *Y. ZHENG[1], W. YIN[2], W. LIN[3];
[1]Lampe Joint Dept. of Biomed. Engineering, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Univ. North Carolina @ Chapel Hill, Chapel Hill, NC

Abstract: Background We applied Network Control Theory (NCT) to uncover the brain energetic landscape across lifespan. NCT derives Average Controllability (AC) quantifying capacity to drive low-energy distributed state transitions, Modal Controllability (MC) reflecting ability to access difficult-to-reach states, Transition Energy (TE) estimating minimal energy for state transitions, and Time-Averaged Control Energy (TCE) representing empirically weighted transition costs. **Methods** We leveraged BCP, HBN, HCP-D, HCP, and HCP-A cohorts (N=1,735; age 0-100+). Structural connectomes were reconstructed via diffusion MRI tractography (MRtrix3/SIFT2). Seven canonical networks (Schaefer-200/Yeo-7) were evaluated. Network centroid states were derived from z-scored resting-state BOLD activity; pairwise TE and transition probabilities were computed between all centroid-state pairs. GAMs with ComBat harmonization characterized lifespan trajectories. For HCP-D, HCP, and HCP-A, age-regressed AC, MC, and TCE were related to NIH Toolbox Total Cognition Composite Score via Partial

Least Squares (PLS) with bootstrap confidence intervals. **Results** Whole-brain AC peaked at ~38 years; MC reached minimum near age 8. Visual and Somatomotor networks showed increasing AC and decreasing MC with age. DMN and Control networks showed rising incoming TE with reduced inflow probability, indicating growing energetic barriers to entry. Salience and Somatomotor networks showed concurrent increases in both TE and inflow probability, remaining comparatively accessible during aging. Permutation testing confirmed significant lifespan shifts (all $p<0.001$). PLS identified Salience AC, Attention MC, and Somatomotor TCE as strongest contributors to Total Cognition, with 95% bootstrap CIs excluding zero. **Conclusion** Aging redistributes neural transition traffic from higher-order association networks toward sensorimotor and salience systems. Network-specific control energetics constitute a key substrate linking structural brain to individual cognitive capacity across the lifespan.



Disclosures: Y. Zheng: None. **W. Yin:** None. **W. Lin:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.01/GG5

Topic: I.05. Working Memory

Title: Functional and anatomical separation of working memory and perceptual decision related signals in dorsolateral prefrontal cortex

Authors: O. CHAUHAN[1], G. NEAL[1], A. SUTTER[3], S. G. SATIRA[2], *S. SHUSHRUTH[4,2]; [1]Neurosci., [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Neurosci., Carnegie Mellon Univ., Pittsburgh, PA; [4]Univ. of Pittsburgh Dept. of Neurosci., Pittsburgh, PA

Abstract: Perception and memory are closely intertwined. During perceptual decision-making (DM), sensory information is often evaluated in the context of other task-relevant information held in working memory (WM). Despite this interdependence, most neurophysiological studies have examined WM and perceptual DM in isolation. To study how mnemonic and sensory information interact during DM, we developed a behavioral paradigm in which monkeys hold a pair of color images in WM, and use them as context to evaluate a subsequent probe image. By parametrically varying chromatic distances between context images and probe image, we dissociate memory- and decision-related signals on a trial-by-trial basis.

We trained two monkeys on the task and both showed integration of memory and sensory information in their decisions. We recorded from multiple dorsolateral prefrontal cortex (dlPFC) subregions in one monkey using Neuropixels probes. We first asked whether WM and DM signals are carried by overlapping or distinct neural subpopulations. Selectivity of single neurons was determined by regressing firing rates on context image color during the memory epoch (WM cells) and on the monkey's choices during the decision epoch (DM cells). Across most recording sites, both subpopulations were present, but their overlap was strikingly low (mean 8.7%, IQR: 1.8-13.5%). We also assessed selectivity by each neuron's contribution to linear decoders of WM or DM. The decoder weights, corrected for cross-neuronal correlations, recapitulated the single neuron result, with a majority of neurons contributing to only one of the decoders.

We next asked whether these subpopulations differ in their laminar distribution. We estimated the laminar location of each unit from LFP spectral profiles (vFLIP algorithm, Mendoza-Halliday et al., 2024). Memory- and decision-selective populations had significantly divergent laminar densities (KS test, $p = 0.02$). Memory-selective neurons were preferentially located in infragranular layers (62.1% in L5/6) compared to decision-selective neurons (41.4% in L5/6; Chi^2 $p = 0.01$).

Together, these results suggest that the integration of WM and DM in dlPFC circuits is primarily implemented by functionally and anatomically segregated populations rather than a homogenous mixed-selective population. Our results offer mechanistic insights into how dlPFC simultaneously maintains memory content while incorporating sensory information to form decisions.

Disclosures: O. Chauhan: None. **G. Neal:** None. **A. Sutter:** None. **S.G. Satira:** None. **S. Shushruth:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.02/GG6

Topic: I.05. Working Memory

Title: Parametric integration of working memory and sensory evidence during perceptual decisions in humans and macaques

Authors: *A. E. SUTTER[1,4], J. WATERS[1,4,5], O. CHAUHAN[6], S. G. SATIRA[6], T. D. VERSTYNEN[1,4,2,3], S. SHUSHRUTH[6,4];
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Abstract: During perceptual decision-making, incoming sensory information must often be assessed in the context of information held in working memory to adaptively guide behavior. Yet decision-making and working memory have primarily been studied as separate cognitive functions, and their interaction is poorly understood. To address this knowledge gap, we developed a behavioral paradigm that parametrically varies both memory content and sensory evidence on a trial-by-trial basis. In each trial, two "context" images, sampled pseudo-randomly from a red-green spectrum, are presented briefly for retention in working memory. After about 1-2 s delay, a probe image whose red-green content falls between the two context images is presented. The subject decides which of the previously presented context images is closer in color content to the probe. The difficulty of the memory component is controlled by the color difference between the two context images (ΔC), and the difficulty of the perceptual discrimination by the offset of the probe color from the midpoint of the context colors (ϵP). Varying ΔC and ϵP independently on a trial-by-trial basis allows us to quantify, within single subjects, how context in working memory influences the evaluation of sensory evidence for perceptual decisions. We collected data from human participants (n=11) and macaque subjects (n=2). In both species, choices varied systematically with ϵP and were well fit by logistic regression. Importantly, logistic slopes increased monotonically across ΔC = 30%, 40% and 50% in both species. In humans, the effect was evident at the population level (rank test on per-subject slopes, mean ranks: $\mu_{30} = 1.36$, $\mu_{40} = 2.09$, $\mu_{50} = 2.55$, 95% CI = [1.55, 2.45]). In macaques, the interaction of ϵP and ΔC in the logistic model was significant individually (NHP 1: $\beta_{\epsilon P \times \Delta C} = 0.3$, $p < 0.001$. NHP 2: $\beta_{\epsilon P \times \Delta C} = 0.08$, $p = 0.015$). Reaction times in both species also scaled jointly with ΔC and ϵP, consistent with a deliberative decision process in which decision difficulty depends on both the memory and sensory components of the task. These results demonstrate a shared cognitive strategy for integrating working memory with perceptual decision-making across humans and macaques, and open an avenue to investigate its neural basis through electrophysiology in macaques and fMRI in humans.

Disclosures: A.E. Sutter: None. **J. Waters:** None. **O. Chauhan:** None. **S.G. Satira:** None. **T.D. Verstynen:** None. **S. Shushruth:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.03/GG7

Topic: I.05. Working Memory

Support: NIH R01 EY017077

Title: Millisecond-precision communication in the frontoparietal network

Authors: A. KARIMI[1], K. BANAIE BOROUJENI[2], Z. WANG[1], A. COMPTE[3], T. WOMELSDORF[1], *C. CONSTANTINIDIS[1];
[1]Vanderbilt Univ., Nashville, TN; [2]Princeton Univ., Princeton, NJ; [3]IDIBAPS, Barcelona, Spain

Abstract: Working memory requires distributed cortical networks to maintain and flexibly rout information as task demands change. Prefrontal (PFC) and posterior parietal cortex (PPC) are both critically involved in this process, but how communication between them dynamically reorganizes during encoding, maintenance, and action remains unclear. Here, we combined macaque single-neuron recordings and computational modeling to examine task-dependent dynamic routing in the PFC-PPC network at the timescale of synaptic communication. We used extracellularly recorded neural signal using 128-channel laminar probes from PFC and PPC simultaneously. The dataset included 2,300 high-confidence single units recorded across 18 sessions from two monkeys. To quantify coordinated spiking interactions, we computed spike-triggered multiunit activity (stMUA) by aligning multiunit activity on one probe to spikes recorded from the same or the other area, allowing us to measure both within-area and interareal interactions. stMUA revealed dominant PFC-to-PPC routing during stimulus encoding and maintenance, followed by a switch to PPC-to-PFC routing during response execution. Directionality was quantified as interareal lead-lag bias, defined as the center-of-mass (COM) timing difference between PFC-to-PPC and PPC-to-PFC stMUA within a 30-ms window. This bias was significant during stimulus encoding (ΔCOM=+3.2±0.7 ms, $P<0.001$); maintenance: +3.1±0.5 ms, $P<0.001$); and action (−2.8±1.0 ms, $P=4.84\times10^{-3}$). This routing bias was reduced during stimulus encoding and maintenance on error trials ($P<0.001$ and $P<0.01$, respectively). Reduced-rank regression identified communication subspaces, defined as source-population activity dimensions that best predicted target-population activity. Different subspace dimensions showed different directional preferences. Finally, we built a reciprocally connected two-area spiking network with excitatory and inhibitory populations. Simulated spiking models predicted that reducing recurrent and interareal excitatory coupling would narrow local stMUA kernels. This prediction was supported empirically with ketamine, which reduced within-PFC stMUA kernel width, measured as full width at half maximum (FWHM; the duration of the kernel at 50% of its peak amplitude), in a separate dataset (6.6 vs. 8.3 ms; n = 331 ketamine and 321 control units; Mann-Whitney $P = 1.36 \times 10^{-4}$). Together, these results reveal millisecond-precision frontoparietal communication that changes direction across task phases and suggest that communication subspaces provide a substrate for flexible routing in working memory. Supported by R01 EY017077.

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Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.04/GG8

Topic: I.05. Working Memory

Support: NSF 2120539
NEI T32EY007125
NIMH F31MH141973

Title: Low-frequency phase temporally coordinates multiple working memory operations

Authors: *Y. DING[1], P. CAVANAH[2], I. C. FIEBELKORN[3];
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Abstract: Working memory unfolds over time, yet how different working memory operations are temporally coordinated remains unclear. Building on prior links between low-frequency neural oscillations and working memory maintenance and retrieval, as well as evidence that low-frequency oscillations help coordinate cognitive functions, we tested whether low-frequency neural oscillations bridge and/or differentiate distinct working memory operations. Specifically, we tested whether low-frequency phase was linked to memory accuracy and event-related neural responses across three operations: (i) encoding, (ii) retrieval, and (iii) distractor processing during maintenance. Using EEG in human participants, we found that encoding and retrieval were most strongly linked to memory accuracy through theta phase (~4-7 Hz), measured just prior to each task event. Pre-encoding theta phase also modulated the neural response to memory item onset, suggesting that theta phase influences encoding strength. Critically, the theta phase associated with better memory accuracy differed significantly between encoding and retrieval, consistent with temporally distinct and functionally specific states supporting each working memory operation. In contrast, the influence of distractors on memory accuracy was linked to alpha phase (~8-10 Hz), with distractor occurrence also appearing to re-engage theta-dependent processes associated with encoding and retrieval. Together, these findings suggest that low-frequency neural oscillations provide a temporal framework that bridges multiple operations of working memory.

Disclosures: Y. Ding: None. **P. Cavanah:** None. **I.C. Fiebelkorn:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.05/GG9

Topic: I.05. Working Memory

Title: Cortical interference, hippocampal pattern separation, and cerebellar prediction in working memory

Authors: *J. T. WIXTED[1], C. W. TALLMAN[2], P. N. STEINMETZ[3];
[2]Psychology, [1]UC San Diego, La Jolla, CA; [3]NeurTex Brain Res. Inst., Dallas, TX

Abstract: Working memory models have proliferated since Atkinson-Shiffrin's (1968) foundational distinction between short-term store (STS) and long-term store (LTS). We argue that theoretical coherence can be improved by linking three neural-computational principles: overlapping cortical coding, hippocampal pattern separation, and cerebellar/background-modeling algorithms for prediction. Complementary Learning Systems (CLS) theory and cognitive models of working memory developed independently but converge on a common idea: capacity limits arise when multiple representations are encoded and retrieved from a shared representational space. In CLS, the neocortex uses distributed overlapping codes that support abstraction and generalization but are interference prone; cognitive models make a similar assumption, treating recently encoded items as overlapping codes that interfere and compete during cue-dependent retrieval. The complementary CLS claim is that hippocampus uses sparse, pattern-separated codes for rapid, interference-resistant episodic storage. This cortical-hippocampal contrast provides a neural basis for distinguishing interference-prone STS from interference-resistant LTS. STS is defined as transient, overlapping cortical coding that supports immediate comparison, integration, and manipulation but is interference prone. Like LTS, STS involves cue-dependent retrieval, not simply persistent activity: cues reinstate overlapping cortical representations, and capacity limits emerge as cues become overloaded. LTS is defined as hippocampal pattern-separated indexing of cortical representations, reducing competition and enabling retrieval of specific events. Thus, STS and LTS—not the less precise labels "working memory" and "long-term memory"—are the relevant constructs, consistent with intracranial evidence showing dissociable hippocampal and cortical memory signals across short and long lags. The proposed framework also distinguishes goal-directed control processes, such as attention and rehearsal, from background modeling: continuously operating mechanisms that shape perception, encoding, and retrieval based on prior experience and contextual predictions. Storage-based WM accounts face a longstanding problem: real-time language comprehension integrates input with knowledge and predictions continuously, without deliberate retrieval of each relevant memory. Background modeling processes (often Bayesian) address this problem by operating without goal-directed retrieval. Cerebellar involvement in semantic prediction provides one neural mechanism that may support such processing.

Disclosures: J.T. Wixted: None. **C.W. Tallman:** None. **P.N. Steinmetz:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.06/GG10

Topic: I.05. Working Memory

Support: K12NS129164
NIMH MH122023
NSF OAC-1730655

Title: Phase-burst coupling across frontotemporal areas predicts item-specific short-term memory in humans

Authors: *V. OMELYUSIK[1], S. S. NAIR[1], B. SAHOO[2], N. COWAN[3], B. KUNDU[2]; [1]Electrical Engin. and Computer Sci., [2]Neurosurg., [3]Psychological Sci., Univ. of Missouri, Columbia, MO

Abstract: Neurons in prefrontal and sensory areas show persistent firing related to preferred items in short-term memory (STM), but the spatial organization of these representations across the brain and the underlying maintenance mechanism remain unclear. Here we present evidence that item-specific information can be decoded from mesoscale field potential data derived from intracranial electrodes. We analyzed data from 6 epilepsy patients as they performed a load-1 object STM task. We considered 22 frontotemporal regions of interest. For each site pair across regions, we extracted the average delay-period high gamma (70-140 Hz) burst duration and amplitude from site 1, and the beta (12-20 Hz) phase from site 2 during bursts of site 1. We trained a non-linear random-forest classifier to solve three classification problem types based on possible mechanisms of discrete information storage in cortex: one-vs-one (distinguish item 1 from item 2; OVO; 36 total), one-vs-rest (distinguish item 1 from rest of items; OVR; 9 total), and multiclass (distinguish item 1 from item 2 from item 3, etc; Multi; 1 total) - and identified predictive pairs (AUC ROC greater than chance on repeated stratified K-Fold cross-validation; $p < 0.05$, Wilcoxon test). Overall, 2318 (88%) pairs in OVO, 1786 (68%) in OVR, and 436 (17%) in Multi were found predictive. We summarized predictive ability of each pair with a synthetic discrimination index and classified pairs into 4 classes: (1) pairwise discriminators; (2) concept-like; (3) low-order-mixed-selective; (4) high-order-mixed-selective. Distributions of these classes across regions matched theoretical expectations, e.g., prefrontal-mesial temporal cortex pairs best fit the concept model while prefrontal cortical pairs fit a mixed-selectivity profile. To assess how a single channel pair might support multiple items, we applied SHapley Additive exPlanations (SHAP) to evaluate feature importance. Preliminary results suggest that phase features tend to be more informative than burst features. Collectively, these observations provide mesoscale insight into the neural mechanisms that may support item storage in STM.

Disclosures: V. Omelyusik: A. Employment/Salary (full or part-time):; Kundu Lab, University of Missouri, Columbia. **S.S. Nair:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIMH MH122023, NSF OAC-1730655. **B. Sahoo:** A. Employment/Salary (full or part-time):; Kundu Lab, University of Missouri, Columbia. **N. Cowan:** None. **B. Kundu:** 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.; K12NS129164.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.07/GG11

Topic: I.05. Working Memory

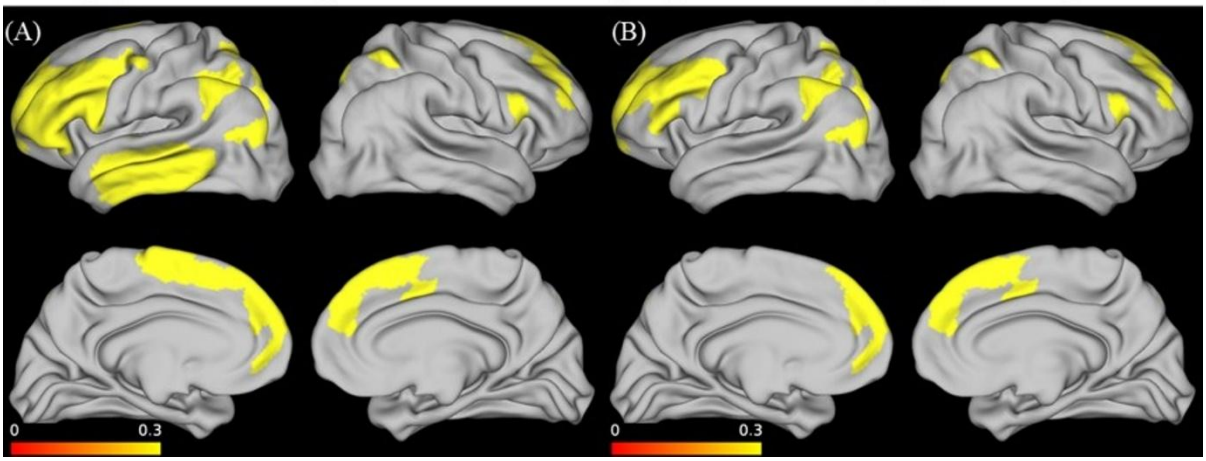
Support: NIDCD T32DC017703
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Title: Language, working memory, and attentional networks are functionally connected during language processing

Authors: *J. BAILEY[1], S. HIMI[3], J. CRUTCHER[4], N. COWAN[1], I.-M. EIGSTI[5], M. STEVENS[6], C. LARSON[2];
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Abstract: Background. Working memory involves maintaining information in a highly accessible state to support ongoing cognitive processes . It is crucial to language processing, yet the neural correlates of this relationship are unknown. This study describes functional connectivity of language-related brain regions with working memory and attention regions in a large cohort of healthy adults. Methods. We analyzed Human Connectome Project data from n = 1,015 (53.4% women) young adults. Regions of interest were based on prior literature (e.g., Baker et al., 2018), reflecting language, working memory, and dorsal/ventral attention networks. Working memory behavior was measured by a List Sorting task and attention behavior by the Short Penn Continuous Performance Test. We calculated connectivity via non-parametric Spearman correlations. We analyzed connectivity using Bayesian linear regression models, predicting average connectivity between or within networks from list sorting or sustained attention performance, controlling for age, sex, and handedness. Results. Strikingly, connectivity was observed among all networks; however, it was not associated with behavioral performance. Connectivity between language and attention networks was observed only in models that did not include attention behavioral performance. A detailed examination showed a skewed pattern in which good attention capabilities were common and could co-exist with any level of connectivity, but unusually poor attention capabilities consistently corresponded to low connectivity. Conclusions. This work supports the assertion that distributed networks and multiple cognitive processes give rise to language, and distributed networks are a fundamental characteristic of complex cognition. Yet, connectivity within and between networks did not generalize to individual differences in behavioral performance outside of the scanner. Future studies should examine additional connectivity metrics and more targeted measures of behavior that may better explain brain patterns underlying surface behavior.

Figure 1. β coefficient representing non-parametric Spearman correlations for (A) language and working memory network connectivity, and (B) within-working memory network connectivity. Yellow indicates relatively positive connectivity and red indicates relatively negative connectivity (not pictured here).



Disclosures: J. Bailey: A. Employment/Salary (full or part-time):; University of Missouri. **S. Himi:** A. Employment/Salary (full or part-time):; Jagannath University. **J. Crutcher:** A. Employment/Salary (full or part-time):; University of Connecticut. **N. Cowan:** A. Employment/Salary (full or part-time):; University of Missouri. **I. Eigsti:** A. Employment/Salary (full or part-time):; University of Connecticut. **M. Stevens:** A. Employment/Salary (full or part-time):; Yale Medical School, Institute of Living. **C. Larson:** A. Employment/Salary (full or part-time):; University of Missouri. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); ERC Synergy Grant; MU Internal Funds.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.08/GG12

Topic: I.05. Working Memory

Title: Information Integration in Working Memory

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Abstract: Understanding how the cognitive system integrates discrete sensory inputs into coherent representations is a central question in psychology, and working memory (WM) plays a key role in this process. While most WM research has centered on the storage and executive control of information, the mechanisms underlying integration itself remain largely unexplored. Here, using confirmatory factor analysis, cognitive load manipulations, and resting-state and task-based functional magnetic resonance imaging (fMRI), we demonstrate that integration

constitutes an independent component within WM, termed the integration buffer. Behaviorally, confirmatory factor analysis revealed that this component could not be attributed to any established component (e.g., visuospatial sketchpad, central executive, or episodic buffer), and cognitive load manipulations selectively targeting these established components did not affect integration buffer performance, providing converging evidence for its independence. At the neural level, functional connectivity-based prediction, brain network analysis, and task activation consistently demonstrated that the integration buffer possesses distinct neural correlates: rather than relying on any single network, it emerged from cooperative interactions between the frontoparietal network (FPN) and the default mode network (DMN), with both networks engaged during active integration. Taken together, these findings support the existence of a distinct integration buffer that integrates discrete elements into coherent unified representations, offering critical insight into the neural mechanisms of working memory.

Disclosures: F. Zhu: None. **Q. Zhou:** None. **J. Wu:** None. **H. Zhou:** None. **Y. Hu:** None. **Z. Gao:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.09/GG13

Topic: I.05. Working Memory

Support: NIH Grant MH129042

Title: Semantic activation disrupts the behavioral efficacy but not the neural engagement of working memory suppression

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Abstract: Semantic activation benefits working memory retention and retrieval, but this facilitation may become a liability when the goal is to remove unwanted information. Removing information from working memory is essential for managing its limited capacity and sustaining goal-directed behavior. The most effective strategy, termed “suppression”, is to push an item out of mind, which reduces immediate access to that information and facilitates the encoding of related information (Kim et al., 2020). Furthermore, greater neural engagement of suppression, measured via MVPA of fMRI data, is linked to worse long-term memory performance for suppressed items (Bretton et al., 2024). Evidence from these prior studies suggest that suppression removes individual items without disrupting related memoranda by selectively targeting item-specific neural features and sparing shared semantic representations, allowing category-level activation to persist regardless of suppression engagement. However, these studies have largely avoided semantic overlap by drawing items from different categories, leaving

untested whether shared meaning strengthens semantic activation and makes removal harder. To address this gap, we tested whether manipulating semantic relatedness among memoranda disrupts the neural engagement of suppression and reduces its behavioral efficacy. On each trial, participants (N=34) encoded four images drawn from two categories, with semantic activation manipulated via presentation order: three consecutive same-category images (high semantic activation) or alternating category exemplars (low semantic activation). They are then cued to either maintain or suppress one of the items, before finally responding to a recognition memory probe. Supporting our hypothesis, suppression reduced accuracy under low semantic activation ($p=0.017$, $BF_{10}=4.76$) but was ineffective under high semantic activation ($p=0.20$, $BF_{10}=0.40$). We also report the first successful decoding of maintenance and suppression from EEG, using frequency band power across 64 electrodes in 400 ms time bins. Despite clear behavioral differences, suppression engagement was statistically equivalent between conditions ($p=0.84$, $BF_{10}=0.185$). These findings reveal a dissociation between the neural engagement of suppression and its behavioral efficacy, pointing to a specific failure mode: suppression operates orthogonally to semantic activation, engaging fully but failing to overcome the representational strength of semantically related items. These results advance our understanding of how semantic context constrains the neural mechanisms of working memory control.

Disclosures: E. Leung: None. **J.A. Lewis-Peacock:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.10/GG14

Topic: I.05. Working Memory

Title: Large-Scale Mapping of Verbal Working Memory Maintenance and Retrieval

Authors: *N. SHI[1], D. G. SOUTHWELL[2], G. A. GRANT[1], B. FRAUSCHER[1], G. B. COGAN[3]; [2]Neurosurg. and Neurobio., [3]Dept. of Neurosurg., [1]Duke Univ., Durham, NC

Abstract: Verbal working memory is essential for learning and communication. While prior work has implicated several regions in supporting verbal working memory, the large-scale network underlying this process remains unresolved. To characterize the spatiotemporal dynamics of verbal working memory with high spatial and temporal resolution, we recorded from stereo-electroencephalography (sEEG) in 68 epilepsy patients (35 F, mean age=31), undergoing monitoring to guide surgical treatments. Participants encoded auditory sequences of words or pseudo-words at varying memory loads (3, 5, 7, or 9 items) and after a maintenance period of around 3 seconds, judged whether a probe matched any item in the sequence. Behaviorally, increasing memory load reduced sensitivity and accuracy and prolonged reaction times, confirming graded working-memory demands. We analyzed high-gamma activity (HGA; 70-200 Hz) from 12,075 implanted electrodes and identified 4,776 with significant task-related activation. HGA mapping revealed a HG activation in a distributed cortico-hippocampal network

spanning superior temporal sulcus and gyrus (STS/STG), prefrontal cortex (PFC), and hippocampal regions. Critically, these nodes exhibited distinct temporal profiles: STS/STG was strongly engaged during auditory encoding, hippocampal regions showed sustained activity throughout the maintenance period, and PFC was preferentially recruited during probe evaluation and response. Using multivariate decoding, we further showed that HGA patterns during maintenance tracked memory load, and during the probe period distinguished whether the probe item had been retrieved, demonstrating that this distributed network represents both the demands and contents of verbal working memory. Together, these findings reveal that verbal working memory is supported by a temporally organized cortico-hippocampal network in which language, memory, and control regions make dissociable contributions across distinct processing phases.

Disclosures: N. Shi: None. **D.G. Southwell:** None. **G.A. Grant:** None. **B. Frauscher:** None. **G.B. Cogan:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.11/GG15

Topic: I.05. Working Memory

Title: Category-Specific Neuronal Sequences in the Human Anterior Temporal Lobe During Stimulus Encoding Support Working Memory

Authors: *U. F. E. HORN[1], I. M. BRIGHT[2], V. SREEKUMAR[2], O. E. FRUCHET[3], S. INATI[2], K. A. ZAGHLOUL[4];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, [3]Neurosurg., [2]NIH, Bethesda, MD; [4]NINDS, Bethesda, MD

Abstract: Working memory (WM) is the brain's ability to temporarily hold and manipulate information over a short period of time. WM was initially believed to be supported by persistent spiking activity, but recent studies have shown this activity to be intermittent, alternating between discrete periods of high firing to silence. Here, we used intracranial microelectrode array recordings in participants with drug-resistant epilepsy to investigate the spiking activity of populations of neurons in the anterior temporal lobe during a WM task. We find that population spiking organizes into bursts of activity while participants actively view to-be remembered items and during delay periods when participants are internally maintaining the previously presented stimulus. These spiking bursts are significantly more prominent during the encoding and delay periods than during rest or the intertrial intervals. Based on recent evidence that the sequential order of activity within these spiking bursts represents the category of actively viewed stimuli (Xie et al., 2024), we investigated whether the spiking bursts observed here maintain WM representations during stimulus presentation and the delay period. We find that the temporal order of unit firing within bursts during active stimulus viewing is significantly more similar

within stimulus categories than across categories. Finally, we investigate the temporal order of spiking as well as the patterns of firing rate activity in bursts that arise during active viewing and the bursts that arise during the memory delay period and the relation between them. Together, our data demonstrate how discrete bursts of population spiking in the anterior temporal lobe support WM performance.

Disclosures: U.F.E. Horn: None. **I.M. Bright:** None. **V. Sreekumar:** None. **O.E. Fruchet:** None. **S. Inati:** None. **K.A. Zaghloul:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.13/GG17

Topic: I.05. Working Memory

Support: National Institute of Mental Health Intramural Research Program ZIAMH002783

Title: Medial temporal lobe involvement in a dual retrocue working memory task

Authors: *C. WALSH[1], M. SMITH[2], J. GONZALEZ-CASTILLO[2], D. A. HANDWERKER[2], T. MORGAN[3], P. BANDETTINI[2,3];
[2]Section on Functional Imaging Methods, [3]FMRI Core Facility, [1]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Maintenance of information in working memory (WM) is fundamental to higher-order cognition and has traditionally been linked to persistent neural activity in the lateral prefrontal cortex. Recent work has suggested that information can be maintained in the face of interruptions to this persistent activity, a phenomenon known as *activity silent working memory*. Here, task relevant information is held through persistent, recurrent activation in parietal and prefrontal regions. Information that is not currently task relevant but may later become so is held in a long term memory state. This process involves sub-threshold patterns of reinforced synaptic weights that are brought into an active supra-threshold state by medial temporal lobe (MTL) structures when they become task relevant.The current work tests whether MTL structures support WM using a dual retrocue task scanned at 7T fMRI (3D EPI BOLD; 1.3mm^3 voxels, TR=1s, TE=10ms). In this task, 9 participants (5F) are initially shown a face and a scene to maintain across a short delay. A cue indicates which image will initially be tested, followed by a probe. A second cue then indicates which image will be tested in the second half of the trial. Critically, this second probe image is sometimes the same image category as the first probe (“stay” trials) and other times reflects the other image category (“switch” trials).Preliminary univariate analyses showed increased activation after the second cue on switch trials in left perirhinal cortex, consistent with retrieval of the initially unattended item (UMI) from a long term memory state. In parallel, a cross-validated multivariate decoder was trained on independent data to distinguish between faces, scenes and objects and subsequently applied to each time point of the

dual retrocue task to index the probability that each category was being maintained. These analyses revealed increased representation of the UMI after the second cue on switch trials in left posterior hippocampus. In contrast, left anterior hippocampus and left perirhinal cortex showed increased representation for the UMI regardless of trial type, suggesting these regions may bind memoranda during encoding and the second cue refreshes the bound information before recall.Together, these findings suggest that MTL structures may support WM without the sustained activation often associated with maintenance. Instead, they may recruit long term memory mechanisms to preserve information that is not immediately task relevant. Future work will assess representations in hippocampal subfields, category agnostic processes in MTL regions, and relationships between hippocampal processes and post-scan memory.

Disclosures: C. Walsh: None. **M. Smith:** None. **J. Gonzalez-Castillo:** None. **D.A. Handwerker:** None. **T. Morgan:** None. **P. Bandettini:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.14/GG18

Topic: I.05. Working Memory

Support: NIH Grant 1R01MH131678-01A1

Title: Representational Dynamics of Prioritization in Working Memory: RNN Simulations

Authors: *J. HUR[1], J. M. FULVIO[2], B. R. POSTLE[3];
[1]Univ. of Wisconsin-Madison, Madison, WI; [2]Psychology and Psychiatry, Univ. of Wisconsin - Madison, Madison, WI; [3]Psychology and Psychiatry, Univ. of Wisconsin–Madison, Madison, WI

Abstract: Updating the relative priority of concurrently held items in working memory is crucial for goal-directed behavior. To study this mechanism, we trained recurrent neural networks (RNNs) to perform a double-serial retrocuing (DSR) task that unfolded as follows: presentation of stimulus 1 (P1), ISI, P2, delay 1.1 (D1.1), Cue1, D1.2, Recall1, D2.1, Cue2, and Recall 2. To visualize stimulus representational geometry and the effects of prioritization, we applied demixed (d)PCA to the hidden layers of the RNNs and derived dimensionality reduced subspaces, which confirmed that stimulus identities were represented on ring manifolds that preserved the metric properties of the stimuli. Initially, stimulus 1 (S1) transitioned through a series of epoch-specific subspaces, the first two of which were subsequently occupied by S2. During D1.1 the two items were arranged on planes separated by an angle of 81.9º, their ordinal context encoded chronologically. The onset of Cue1 was accompanied by the emergence of an item-by-priority interaction (iXp) axis that expanded across the epoch, and along which the two stimulus manifolds geometrically stratified in a cue-dependent manner. Over the course of Delay1.2 the relative geometry of the S1 and S2 manifolds reconfigured along a stimulus-by-

priority interaction (sXp) axis, such that the prioritized and deprioritized items came to occupy consistent "template" configurations within this subspace, while retaining an angle of separation of 65º. Following Recall1, during D2.1, the two manifolds returned to configurations qualitatively similar to those from D1.1, with an angle of separation of 73º. Cue2 and D2.2 produced dynamics qualitatively similar to those from Cue1 and D1.2. Finally, during Recall2, the polygonal area of the uncued item (now an "irrelevant memory item," IMI) collapsed dramatically to a (unitless) value of roughly 0.1 (relative to the cued item's value of roughly 1000). These results provide a normative model of the dynamics of prioritization in working memory against which, in the companion poster from Fulvio, Hur, and Postle, we evaluate EEG data from humans performing this task.

Disclosures: J. Hur: None. **J.M. Fulvio:** None. **B.R. Postle:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

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Topic: I.05. Working Memory

Support: NIH Grant 1R01MH131678-01A1

Title: Representational Dynamics of Prioritization in Working Memory: Human EEG

Authors: *J. M. FULVIO[1], J. HUR[2], B. R. POSTLE[3];
[1]Univ. of Wisconsin - Madison, Madison, WI; [2]Neurosci., Univ. of Wisconsin-Madison, Madison, WI; [3]Psychology and Psychiatry, Univ. of Wisconsin–Madison, Madison, WI

Abstract: Sixteen participants performed a double serial retrocuing (DSR) task that unfolded as follows: presentation of stimulus 1 (P1), ISI, P2, delay 1.1 (D1.1), Cue1, D1.2, Recall1, Cue2, D2, and Recall 2, plus a matched task with neutral cues (NEU). The EEG data were analyzed to test hypotheses derived from the RNN simulations reported in the companion poster from Hur, Fulvio, and Postle. In both tasks, results from the initial P1-ISI-P2-D1.1 epochs indicated that, as with RNNs, S2 followed the same perception-to-memory trajectory as had S1, resulting in a chronological encoding of ordinal context during D1.1. First, polygonal area of stimulus manifolds in demixed (d)PCA-derived subspaces indicated that, during P2, the separability of S2 projected into the P1 subspace at S2 presentation was significantly above chance, whereas S1 during that epoch was significantly better captured by a new subspace. Second, during D1.1, S1 was significantly better captured by a new subspace than by the ISI subspace it had previously occupied. With the onset of Cue1, in both DSR and NEU, items separated along a cue axis that expanded during the cue epoch (both, $p \leq .0001$), then contracted during D1.2. Also during D1.2, only for DSR, the prioritized and unprioritized items systematically reorganized around a newly-emerged stimulus x priority (sXp) axis, with shorter latency when S1 had been cued, whereby both prioritized items occupied positive positions along the axis relative to the negative positions

occupied by both deprioritized items (both $p \leq .013$). As with Cue1, Cue2 onset triggered separation along a cue axis ($t(15) = 5.48$, $p = .0001$), but unlike D1.2, sXp reorganization did not re-emerge at D2 (all $p > .15$). These results confirm that, as with RNNs, the dynamics of the human EEG can be understood as a trajectory through epoch- and priority-specific configurations of latent dimensions. Further work is needed to reconcile this perspective with the large body of evidence from decoding analyses that priority coding disproportionately influences the unprioritized item.

Disclosures: J.M. Fulvio: None. **J. Hur:** None. **B.R. Postle:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

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Program #/Poster #: PSTR109.16/GG20

Topic: I.05. Working Memory

Title: Human primary somatosensory cortex is inhibited during vibrotactile working memory

Authors: *V. SONI[1], A. ABDALTAWAB[1], A. PERSELLO[1], R. A. GAUNT[2], C. M. GREENSPON[3], D. MENDOZA-HALLIDAY[1];
[2]Physical Med. and Rehabil., [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Dept. of Organismal Biol. & Anat., Univ. of Chicago, Chicago, IL

Abstract: Humans and many other species can temporarily maintain and manipulate mental representations of recent sensory stimuli, an ability known as working memory (WM). This ability is thought to depend on sensory association areas and higher-level parietal and prefrontal cortical areas, where neurons show sustained activity selective for memorized sensory stimulus properties. One issue that remains unresolved is whether the maintenance of sensory WM representations also depends on the activity of neurons in early sensory cortical areas. This controversy is largely due to the discrepancy between fMRI studies in humans - claiming an involvement of these areas in WM maintenance, and single neuron-level electrophysiological studies in non-human primates - claiming no involvement. To bridge this apparent discrepancy between studies that used different recording methods in different species, here we recorded single neuron spiking activity and local field potentials (LFPs) from human primary somatosensory cortex (S1) during a vibrotactile WM task. In each trial, we presented a 1.2-s sample vibrotactile stimulus, followed by a 5-s delay (with a 1s distractor stimulus mid-delay) during which the sample amplitude had to be maintained in WM. A test stimulus was then presented for 1.2 s, and the task required reporting which amplitude was higher - sample or test. In a majority of recorded neurons, firing rates increased during the sample presentation and were selective for the sample amplitude - confirming the known sensory encoding role of these neurons. In contrast, after sample offset, firing rates decreased and remained below baseline throughout the entire delay (except during the distractor). S1 inhibition during the delay was also observed in the dynamics of LFP activity, with gamma power remaining below baseline and beta

power remaining above baseline throughout the delay. For both firing rates and LFP power, the signatures of inhibition became stronger throughout the delay, as the trial approached the test stimulus. Importantly, neither neuronal firing rates nor LFP power in any band encoded the memorized sample amplitude, confirming the lack of involvement of S1 neuronal activity in WM maintenance. Together, these results suggest that human S1 is actively inhibited during the maintenance of somatosensory representations in WM, which may reflect a sensory gating mechanism in which higher-order cortical areas suppress early cortical sensory processing stages to mitigate the detrimental effect of sensory interference on WM maintenance.

Disclosures: V. Soni: None. **A. Abdaltawab:** None. **A. Persello:** None. **R.A. Gaunt:** None. **C.M. Greenspon:** None. **D. Mendoza-Halliday:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.17/GG21

Topic: I.05. Working Memory

Support: Internal lab funds

Title: Trial-Level Oscillatory Predictors of Response Time in Auditory Working Memory: A State-Space ERP Approach

Authors: *F. WERNSTAAL[1,2], P. L. PURDON[3];
[1]Stanford Univ., Stanford, CA; [2]Karolinska Institutet, Stockholm, Sweden; [3]Stanford Univ. Sch. of Med., Palo Alto, CA

Abstract: Conventional EEG analyses average across trials, discarding the trial-by-trial neural variability that couples oscillatory dynamics to behavior. We applied a state-space ERP (ssERP) framework — which separates evoked responses from induced oscillatory components via expectation-maximization and yields per-trial oscillatory variance (σ^2) — to test whether trial-level oscillatory power predicts working memory response time (RT) in ways inaccessible to trial-averaged analyses.
Two participants (P1: male, 32, 10 sessions; P2: female, 29, 2 sessions) completed 12 EEG sessions of an auditory N-back task (0-, 1-, 2-back), recorded with an ANT Neuro 128-channel cap and eego™hub amplifier. ssERP was fit at 16 sites spanning frontal, central, motor, parietal, and occipital cortex. Spearman σ^2-RT correlations were computed per session for theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and broadband (1-50 Hz) in stimulus, post-stimulus ITI, and full-trial windows; cross-session consistency was tested via Wilcoxon on Fisher-z values. Stimulus-window oscillation negatively predicted RT at 1-back (alpha $r=-0.13$, $p=0.001$; broadband $r=-0.12$, $p=0.0005$), with a marginal broadband effect at 2-back ($r=-0.05$, $p=0.052$) and no effect at 0-back — a load-tuned coupling. For broadband at 1-back, the effect was frontal-dominant and bilateral, with motor electrodes ranked 9th and 12th of 16 — arguing against a

movement confound; alpha showed a broader distribution including centroparietal sites. Critically, the same bands showed an opposite-sign coupling in the post-stimulus ITI at 1-back (broadband r=+0.11, p=0.021; alpha r=+0.11, p=0.064 trend): within the same trial, stimulus-window oscillation tracked faster responses while post-stimulus oscillation tracked slower responses, consistent with state-dependent engagement and disengagement.
Beta-RT coupling was strongest at 2-back ($r \approx -0.10$, $p<0.01$), but comparable effects at motor-adjacent electrodes preclude confident interpretation. Theta oscillators were not resolved at frontal electrodes. ssERP evoked waveforms showed load-dependent ERP changes (monotonic LPC amplitude increase at ~CP3, Friedman p=0.009; frontocentral LPC latency shortening, FCz $\Delta \approx 42$ ms, p=0.029).
These findings show that ssERP per-trial σ^2 resolves time-window-specific oscillation-RT coupling — opposite signs at stimulus and post-stimulus windows in 1-back — not recoverable from trial-averaged analyses; data collection is ongoing.
As pilot data from two participants (10 and 2 sessions respectively), statistical claims reflect cross-session consistency rather than between-subject inference.

Disclosures: F. Wernstaal: None. **P.L. Purdon:** Other; PLP is a cofounder of PASCALL Systems, a startup company developing closed-loop physiological control for anesthesiology..

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

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Program #/Poster #: PSTR109.18/GG22

Topic: I.05. Working Memory

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Title: Neural Correlates of trial-to-trial variability in memory-guided saccadic eye movements during visuospatial task performance

Authors: *J. TEPAN[1], A. KHIBOVSKA[2], T. MORTON[2], H.-C. LEUNG[2];
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Abstract: Visuospatial working memory and oculomotor response control involve a distributed network of cortical and subcortical regions. However, the relationship between neural activity in these regions and trial-to-trial variation in cognitive and eye movement responses remains unclear. To examine this relationship, we related trial-to-trial fMRI signal to visually and memory-guided saccadic eye movements. A group of 28 young adults (F=20; aged 18-33) performed visuospatial working memory and oculomotor control tasks across multiple runs, with 16 trials per run. In the memory-guided saccade (MGS) task, a peripheral target was briefly presented at the beginning of each trial, and after a 2- or 5-s delay, a shift in eye gaze was

required to the remembered location. In the sequential memory guided saccade (sMGS) task, four targets were presented sequentially, followed by an 8- or 10-s delay; and after a cue was displayed, a shift in eye gaze was required to the location of the cued item. In the visually guided saccade (VGS) task, a shift in eye gaze was required as soon as the target appeared. Memory performance was measured using saccade precision and latency, and oculomotor performance using saccade amplitude and velocity. Eye movements were recorded using an EyeLink 1000 system and processed with custom MATLAB scripts to extract trial-level saccade metrics. Structural and functional MRI images were acquired using a 3T Siemens Prisma system and preprocessed using HALFpipe. First-level general linear models and parametric analysis were used to estimate the association between variation in BOLD signal and variation in oculomotor performance during each task epoch. Second-level models were utilized to examine these performance-related activation patterns for the whole cohort. Overall, our results align with prior visuospatial working memory and oculomotor control studies, showing activation of the dorsolateral prefrontal cortex, superior frontal sulcus, precentral sulcus, frontal eye fields, and intraparietal sulcus during the MGS and sMGS tasks. Further, parametric variability is associated with distinct brain activity patterns depending on the task. During the delay and response epochs of MGS, longer saccade latency is associated with a weaker BOLD signal in working-memory-related regions. During the response period, saccade amplitude and velocity showed an association with posterior parietal and visual regions. A similar but weaker effect was found for the delay epoch of sMGS. Overall, these results suggest a potential dissociation between the neural correlates of memory-related and oculomotor components of saccade response variability.

Disclosures: J. Tepan: None. **A. Khibovska:** None. **T. Morton:** None. **H. Leung:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.19/GG23

Topic: I.05. Working Memory

Support: HHMI

Title: A Classification-Based LSTM Decoder Reveals Reward Location Representations during Hippocampal-Prefrontal Delay Activity in a Spatial Working Memory Task

Authors: *L. WANG, J. LEE, A. K. LEE;
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Abstract: Previous work has shown that memory-guided navigation requires the joint contribution of the hippocampus and the medial prefrontal cortex (mPFC). However, in classic delayed non-match to place (DNMP) T-maze tasks, activity patterns that consistently distinguish between goal conditions have not been found in either region when the delay is sufficiently long. Here, we investigated large-scale hippocampal and mPFC activity in a DNMP T-maze task. In

each trial, the animal was forced to visit one arm during a sample phase, then required to wait in an enclosed home area for 20 s, and finally needed to choose the opposite (non-matching) arm to receive a reward. We chronically implanted two Neuropixels probes to simultaneously record from the hippocampus and mPFC in freely moving mice, obtaining ~150 and ~300 neurons per area, respectively. Shuffling confirmed that the animals' home area occupancy patterns did not differ significantly between goal contingencies, implying that they primarily relied on internally stored information to perform this task. During the delay, there was not a significant number of individual neurons whose firing rates coded for the goal conditions. Furthermore, population-level classifiers (Support Vector Machines, Multilayer Perceptron) performed at chance levels. We therefore looked at alternative ways that delay activity patterns could signal information that differed from the animal's current sensory state. We adapted the LSTM-based neural decoder developed by Lai et al. (2023, PMID 37917713), which employed noisy synthetic examples to improve model robustness. Building on this architecture, we developed a new classification-based decoder that has a custom loss function reflecting the maze's 2D geometry and that predicts which spatial bin the animal currently occupies. We trained this decoder on hippocampal or mPFC activity recorded during both inbound and outbound periods when the animal was actively locomoting. Both hippocampal and mPFC activity patterns during periods of immobility in the delay resembled the activity patterns observed during running at the two rewarded goal locations, but not those observed at other maze locations outside the home area, such as the T-maze choice point. This was the case even though all spatial bins were present in a balanced manner during training, making all spatial bins equally likely as a prediction target. We are currently examining whether the decoded locations indicate the goal condition on a trial-by-trial basis.

Disclosures: L. Wang: None. **J. Lee:** None. **A.K. Lee:** None.

Poster

PSTR109: Distributed Mechanisms of Working Memory in Humans and Animals

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR109.20/GG24

Topic: I.05. Working Memory

Support: NIH U19NS104648
NSF Graduate Research Fellowship

Title: Discrete and continuous strategies for parametric working memory

Authors: *J. YANAR[1], J. KAMINSKY[2], C. D. BRODY[3];
[1]Princeton Univ., Princeton, NJ; [2]Princeton Neurosci. Inst., Princeton, NJ; [3]Princeton Neurosci. Inst., HHMI / Princeton Univ., Princeton, NJ

Abstract: While the mechanisms supporting short-term maintenance of binary variables such as left-versus-right choice have been extensively studied, much less is known about how the brain

maintains and manipulates continuous variables. Foundational work in monkeys and rats suggests that such memories rely on a continuous line attractor subject to contraction bias, with representations drifting towards the stimulus mean over time. To test this in mice and open the paradigm to a richer experimental toolkit, we developed a parametric working memory task for head-fixed mice in virtual reality. Mice navigate a T-maze and compare the variable frequencies of two visual gratings, Sa and Sb, separated by a delay. They report whether Sa was lower than Sb by turning left or right. Across single sessions and averaged behavior, choice psychometrics were broadly consistent with a continuous representation of Sa subject to contraction bias. However, high-density silicon probe recordings from the frontal and retrosplenial cortex in an initial subset of animals revealed a different geometry. Rather than scaling continuously as a function of Sa, single-unit tuning and neural population trajectories during the delay period partitioned into distinct “low” and “high” clusters. This suggests that rather than maintaining a precise, graded representation of Sa in working memory, these mice categorized Sa via a low/high judgment, and subsequently applied one of two separate Sb comparison rules to solve the task. To formalize this discrete strategy, we developed a mixture-of-experts choice model and compared it against a simpler logistic model consistent with a continuous line attractor representation of Sa. This revealed behavioral heterogeneity: many mice were better fit by the binarization model, while others favored the continuous one. Strikingly, these distinct strategies were reflected in the animals’ trial-averaged navigational trajectories, providing an independent signature of their cognitive strategy. These results demonstrate that mice can solve the same working memory task using fundamentally distinct algorithms, highlighting the importance of explicitly modeling individual behavior. Ongoing recordings aim to determine whether mice better fit by the continuous model exhibit graded neural representations. Ultimately, our ability to identify continuous and discrete strategies in mice opens the door to strategy-specific causal perturbations, allowing us to manipulate memories online and test maintenance mechanisms across distinct cognitive regimes.

Disclosures: J. Yanar: None. **J. Kaminsky:** None. **C.D. Brody:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.01/HH2

Topic:

Title: Orbitofrontal Hub Dynamics Support Partner-Specific Communication

Authors: *J. M. VINCELLI[1], M. CLACK[1], K. KHAN[2], B. GRAUL[1], J. J. LIN[3], R. T. KNIGHT[4], A. STOLK[1];
[1]Psychological & Brain Sci., Dartmouth Col., Hanover, NH; [2]UPenn MSTP, Philadelphia, PA; [3]UCLA, Los Angeles, CA; [4]UC Berkeley, Berkeley, CA

Abstract: When we communicate, we tailor our behavior to the person we are addressing. For instance, speakers routinely use simpler words and greater emphasis when speaking to a child than to an adult. We hypothesized that translating such partner-specific knowledge into communicative behavior depends on the dynamic coordination of distributed neural systems and that the orbitofrontal cortex (OFC) plays an important role in this process. The OFC is engaged when speakers prepare to communicate with a conversational partner (Kuhlen et al., 2017), and patients with OFC damage often fail to flexibly apply social knowledge to their behaviors despite retaining access to that knowledge (Beer et al., 2006; Stolk et al., 2015). However, direct evidence for how the OFC contributes to large-scale neural coordination during communication has remained limited, in part because the relevant processes unfold rapidly across distributed brain networks. Here, we addressed this challenge by recording intracranial electroencephalography (iEEG) from 22 neurosurgical patients (2,123 electrodes) during an experimentally controlled nonverbal communication task. Participants alternated between communicating with a presumed child and a presumed adult addressee, while a single confederate, blind to the presumed addressee identity, performed both roles with matched behavior. This design isolated neural processes driven by the participants' internal representations of their interlocutor from those driven by differences in actual partner behavior. To test whether the OFC serves as a network hub supporting partner-specific communication, we quantified cross-frequency betweenness centrality, a graph-theoretic measure of a region's role in coordinating information flow across neural networks spanning multiple frequency bands. Consistent with our hypothesis, the right OFC (31 electrodes, 13 participants) emerged as a prominent hub in a brain-wide rank-based permutation analysis (Benjamini-Hochberg FDR $q < 0.001$ across all sampled regions), occupying a central position in this integrated cross-frequency network. Moreover, OFC centrality was selectively elevated during the production of child-directed communicative behavior relative to adult-directed communication, despite identical partner behavior across conditions. Together, these findings identify the OFC as a cross-frequency network hub whose role in large-scale neural coordination varies with the internal representation of a communicative partner, supporting the flexible translation of social knowledge into communicative behavior.

Disclosures: J.M. Vincelli: None. **M. Clack:** None. **K. Khan:** None. **B. Graul:** None. **J.J. Lin:** None. **R.T. Knight:** None. **A. Stolk:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.02/HH3

Topic:

Title: The Orbitofrontal Cortex as a Cross-Frequency Network Hub During Social Interaction

Authors: *M. CLACK[1], J. VINCELLI[1], K. KHAN[2], B. GRAUL[1], J. J. LIN[3], R. T. KNIGHT[4], A. STOLK[1];

[1]Dartmouth Col., Hanover, NH; [2]Univ. of Pennsylvania, Philadelphia, PA; [3]UCLA, Los Angeles, CA; [4]UC Berkeley, Berkeley, CA

Abstract: Everyday communication hinges on the ability to flexibly produce and interpret signals to establish and maintain alignment between communicative partners. This capacity likely depends on the coordinated activity of distributed neural systems, requiring the integration of information across brain circuits as interactions unfold. We reasoned that the orbitofrontal cortex (OFC) may play an important role in this process, as patients with OFC damage often fail to flexibly translate social knowledge into behavior in real time (e.g., Beer et al., 2006; Stolk et al., 2015). Yet direct evidence for how the OFC contributes to such coordination has remained elusive, due in part to difficulties experimentally isolating the neural processes underlying live communication and measuring large-scale network dynamics with sufficient spatial and temporal precision. Here, we addressed these challenges by recording intracranial electroencephalography (iEEG) from 38 neurosurgical patients (4,053 electrodes) performing a dyadic communication task that isolated distinct phases of interaction and manipulated whether communicative partners could rely on established conventions or were required to build conceptual alignment by negotiating novel communicative strategies. To test the hypothesis that the OFC supports communicative interaction through the coordination of distributed neural processes, we quantified multi-frequency betweenness centrality, a graph-theoretic measure of a region's role in mediating information flow across a network. Betweenness centrality analyses identified the OFC as one of the most central nodes within communication-related networks (FDR $q < 0.001$), occupying a prominent position within frequency-specific network architectures, consistent with a cross-frequency hub role. Moreover, OFC centrality was selectively elevated both during the production and interpretation of communicative exchanges, and when participants were required to build alignment rather than rely on previously established communicative conventions. Among highly central regions, the OFC was the only one to exhibit this communicative specificity. Together, these findings identify the OFC as a prominent network hub and suggest that it contributes to communicative interaction by coordinating information across neural circuits in support of alignment between communicative partners.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.03/HH4

Topic: I.06. Social Cognition

Support: ISF (388/24)

Title: Mapping Abstract Neural Representations Through Model Comparison: The Case of (Dis)Belief

Authors: *G. BRAUN[1], Y. YESHURUN[2];
[1]Tel Aviv Univ., Tel Aviv, Israel; [2]Tel Aviv Univ., Tel-Aviv, Israel

Abstract: Belief plays a central role in social life, shaping how individuals evaluate information, form judgments, and interact with others. Using fMRI data collected during the presentation of naturalistic auditory narratives, we examined how (dis)belief is geometrically represented in the brain. Participants (N = 68) listened to six judicial narratives and subsequently rated the extent to which they believed each narrative, ranging from complete disbelief to complete belief. To compare competing representational hypotheses, pairwise neural synchrony matrices were evaluated in a winner-takes-all framework against multiple computational models of inter-subject representational similarity which capture distinct structures of belief representation, including directional (dis)belief position (*fmean*), shared certainty/extremity (*fextremity*), same-side epistemic alignment (*fside*), continuous interpersonal distance (*fdist*), and discrete categorical grouping into belief, uncertainty, and disbelief states (*f3cat*).
Neural synchrony was best explained by two representational dimensions of (dis)belief, both of which showed significant effects following permutation testing and FDR correction. First, a directional belief-disbelief axis (*fmean*) revealed both positive and negative effects across distinct DMN regions, indicating that different neural populations were selectively tuned to opposite poles of the belief continuum. Consequently, pairs of participants sharing disbelief could exhibit reduced synchrony in some regions while showing enhanced synchrony in others. Second, a certainty/extremity model (*fextremity*) explained additional variance in neural synchrony across widespread DMN regions, suggesting that belief representations are also organized along a certainty-related dimension that operates independently of belief direction.
To determine whether neural representations of belief are governed by a single dominant dimension or by multiple representational geometries, we conducted ridge regression analyses separately for each narrative using the upper-triangle vectors of all representational models as predictors of pairwise neural synchrony. Although the directional belief (*fmean*) and certainty/extremity (*fextremity*) dimensions accounted for the largest proportion of explained variance, neural representations were not reducible to a single organizing principle. Instead, multiple representational models contributed unique explanatory power, suggesting that belief-related processing emerges from the interaction of several complementary dimensions organized around belief direction and certainty.

Disclosures: G. Braun: None. **Y. Yeshurun:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.04/HH5

Topic: I.06. Social Cognition

Support: NIMH Grant F30MH135658

Title: Neurocomputational mechanisms of social norm learning in human prefrontal cortices

Authors: *A. DAVIS[1], S. E. QASIM[3], Q. FU[1], F. PANOV[1], X. GU[2], I. SAEZ[1];
[2]Psychiatry, Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [3]Psychiatry, Rutgers Robert Wood Johnson Med. Sch., New York, NY

Abstract: An important skill within social functioning is the ability to learn and adapt to changing social norms, or rules of behavior among social groups. Previous work has conceptualized norms as relatively stable social perceptions. More recently, however, computational modeling of behavior has started to elucidate the dynamic and flexible nature of human norm perception by showing that humans can adjust to changing social environments based on norm prediction errors (nPEs), defined as the difference between a social signal or offering and one's internal expectation (Gu et al., 2015; Na et al., 2021). While computational modeling of behavior has advanced our understanding of how humans learn social norms, little is known about what neural mechanisms support this process. The purpose of this study was to leverage computational modeling in conjunction with human intracranial recording to examine the roles of prefrontal cortices in social norm learning. Here, 23 neurosurgery patients (9 men, 14 women, aged 39.2 ± 3.05 years (mean ± SEM)) with drug-resistant epilepsy played an iterative Ultimatum Game with human and computer avatar partners while undergoing intracranial electroencephalography recording from the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), dorsomedial prefrontal cortex (dmPFC), and anterior insular cortex (AIC). Behaviorally, we found that participants rejected increasingly unfair offers more often and that nPEs influenced their momentary mood. Neurally, the ACC, OFC, and dmPFC encoded trial-by-trial offers. The ACC, dmPFC, and AIC encoded previous outcomes. The dmPFC also encoded current and previous norm violations. At relatively longer timescales, intra-regional coherence in the AIC and dmPFC correlated with higher-level norm learning-related variables, subjective indifference points and initial norms, respectively. Collectively, these findings identify key neural mechanisms underlying social norm learning; specifically, all regions of interest contribute to short-term norm learning by encoding offers, outcomes, and norm violations, while dmPFC and AIC activity further relate to subject-level behavioral parameters that influence norm learning in the long term.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.05/HH6

Topic: I.06. Social Cognition

Support: NIH Grant 5R01MH134990)

Title: Narrative expectations, indexed by LLM embeddings, selectively modulate low-frequency iEEG dynamics during face perception

Authors: ***H. JUNG**[1], U. KELES[2], W. HUANG[1], G. CHEN[3], H. JAIN[4], J. YIH[1], A. MAJUMDAR[1], C. PERRY[1], D. BEAM CUNNINGHAM[5], L. GWILLIAMS[1], J. PARVIZI[6]; [1]Stanford Univ., Stanford, CA; [2]Caltech, Pasadena, CA; [3]Peking Univ., Beijing, China; [4]Univ. of Colorado Boulder, Boulder, CO; [5]New York Univ., New York, NY; [6]Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Expectations about future experiences can significantly shape the way we interact with the external world. For instance, learning that your new neighbor rescues dogs shapes the way we perceive them. Using intracranial EEG, we explore the effects of top-down expectations during face perception and uncover components that are modulated by or insulated from expectations. For a given trial, participants listened to short audio clips briefly describing the characteristic of an upcoming face ("audio") with positive, negative, and neutral valence, then viewed a neutral face for one second ("face"). Using a pre-trained large language model (LLM), we quantify "expectations" by using semantic embeddings of prior information and examine the unique variance explained during face perception. With the growing appreciation towards broadband signals, we investigate both high frequency (HFA) and low frequency activity (LFA). We take a two-step approach. First, using consensus non-negative matrix factorization, we identify data-driven clusters of electrodes based on canonical neural time-series. Second, treating the unbiased clusters as spatial-temporal motifs of HFA and LFA, we implement encoding models with trial-wise LLM embeddings to test whether each cluster is differentially modulated by expectations during face perception. First, with the clustering approach, we find that spatial-temporal motifs in HFA and LFA respond differently to valence information; LFA showed systematic modulation by valence, whereas HFA clusters were primarily sensory-driven and remained insensitive to valence-based narratives. Next, trial-wise semantic embeddings of prior narratives predict face epoch signals selectively in an LFA cluster. Overall, these results suggest that expectations are preferentially carried by LFA, while HFA remains anchored to sensory input. These results advocate for examining the broadband spectrum when investigating context-dependent modulation.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Topic: I.06. Social Cognition

Support: William H. Neukom Institute for Computational Science at Dartmouth College
Waterhouse Research Award

Title: Ambiguous narrative stimuli for differentiating between endogenously- and exogenously-driven neural signals of subjective experience

Authors: *K. DUNCHEVA, K. O'NELL, E. FINN;
Dartmouth Col., Hanover, NH

Abstract: No two people interpret an event exactly the same way, and previous studies show that individuals who come to the same subjective interpretation of an ambiguous stimulus also exhibit synchronized brain activity in default mode network regions. However, past work does not directly contrast signatures of endogenous (e.g., personality traits and internal biases) and exogenous (e.g., priming cues) sources of differential interpretations. To understand how these two pathways to shared or diverging interpretations are instantiated in the brain, we have developed a set of ambiguous narrative stimuli that (a) at baseline, elicit a near-uniform distribution of responses (i.e., subjects are equally likely to endorse either one of two possible interpretations), and (b) with additional context, can be primed toward each interpretation. Here, we validate a dataset of 19 ambiguous narratives through online behavioral experiments on 147 subjects. Participants consisted of 60% women (N=87), 37% men (N=54), 4% other (N=4). Most participants identified as white (54%), followed by Black/African American (30%), mixed race (11%), Asian (3%), Native American (1%), and 1% who did not report race. The mean age was 28 years (SD = 4.9, range 18-35). Each participant was shown 6 ambiguous narratives: 3 neutral, 3 primed. Participants were asked to endorse one of two possible interpretations (coded as 0 and 1), report their confidence, highlight story passages that influenced their interpretation, and answer an attention check. After removing trials with failed attention checks, 86% of trials (756/882) were analyzed. Neutral stimuli elicited a near-uniform distribution of responses with an average confidence-weighted response of 0.53 (SD = 0.13, range 0.3-0.78). When counts of interpretations were compared across conditions with a X^2 test, one narrative elicited significant differences in responses between the neutral and both primed conditions. Six stimuli elicited significant differences in responses between the neutral and one of the primed conditions. For 12 stimuli, the differences in elicited responses across conditions were not significant. However, 17 stories total followed the expected qualitative pattern. Additionally, participants who selected different interpretations also highlighted significantly distinct story elements as motivating evidence (permutation tested Bray-Curtis distance) in 17 of the 19 stories. Upon refinement, these stimuli will allow for brain imaging comparison of neural responses to evidence in favor or against a chosen response and will help disentangle the effects of endogenous and exogenous drivers of subjective experience.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.07/HH8

Topic: I.06. Social Cognition

Support: R01AG075044
R01AG070931

Title: Age differences in regional activity and dynamic functional connectivity during social cognitive judgments in movie-watching

Authors: *R. J. PATEL[1], R. FRENCH[2], C. HUGHES[2], A. KRENDL[2], R. BETZEL[3]; [1]Indiana Univ., Bloomington, IN; [2]Psychological and Brain Sci., Indiana Univ. Bloomington, Bloomington, IN; [3]Dept. of Psychological and Brain Sci., Univ. of Minnesota, Minneapolis, MN

Abstract: Social connectedness plays a key role in delaying older adults' cognitive declines. Though navigating social connections is complex and dynamic (Tamir & Thornton, 2024), the mechanisms underlying these processes have been largely unexplored in older adults. Specifically, it remains unknown whether both regional (nodal) activity and pairwise cofluctuations (edges) contribute to older adults' social judgments. We disentangled their unique contributions using a naturalistic movie-watching task and continuous behavioral judgments acquired post-scan. Young (YA; n=105) and older (OA; n=95) adults viewed two *Nathan For You* episodes, a mockumentary TV show with social interactions, while undergoing fMRI. They then provided continuous joystick ratings of awkwardness post-scan, e.g., (Pantelis et al., 2015). Analyses used the nodes and edges in the 17-network Schaefer nodal parcellation (Schaefer et al., 2018). Edge time series (ETS) were calculated across all unique parcel pairs with a 2-second TR, preserving moment-to-moment co-fluctuations rather than averaging them into static correlations (Faskowitz et al., 2020; Zamani Esfahlani et al., 2020). For each participant, we used ordinary least squares models to predict the hemodynamic response function-convolved awkwardness time course from ETS while covarying constituent nodal time series, e.g., (Merritt et al., 2024; French et al., 2025). Age-group differences were tested with independent-samples t-tests, corrected for multiple comparisons using FDR correction ($q<0.05$), and 10,000 spatial spin permutations (Váša et al., 2018). Nodes and edges each accounted for unique variance in awkwardness ratings for both YA and OA. Similar patterns emerged for both YA and OA, but beta magnitudes were attenuated in OA. Significant group differences were primarily nodal: YA showed stronger positive associations in control-C and stronger negative associations in default-C than did OA. Edge-level group differences were localized to somatomotor-B: YA showed stronger positive co-fluctuation associations linking somatomotor-B to dorsal-attention-A/B and control-A/C, and stronger negative associations linking somatomotor-B to default-C than did OA. These findings suggest that aging preserves the qualitative direction of awkwardness-related neural tracking while weakening the coupling between behavior and both regional activity and time-varying connectivity. Identifying these age-related changes may help clarify neural mechanisms through which altered social perception contributes to reduced social engagement and its downstream consequences for cognitive and emotional health in later life.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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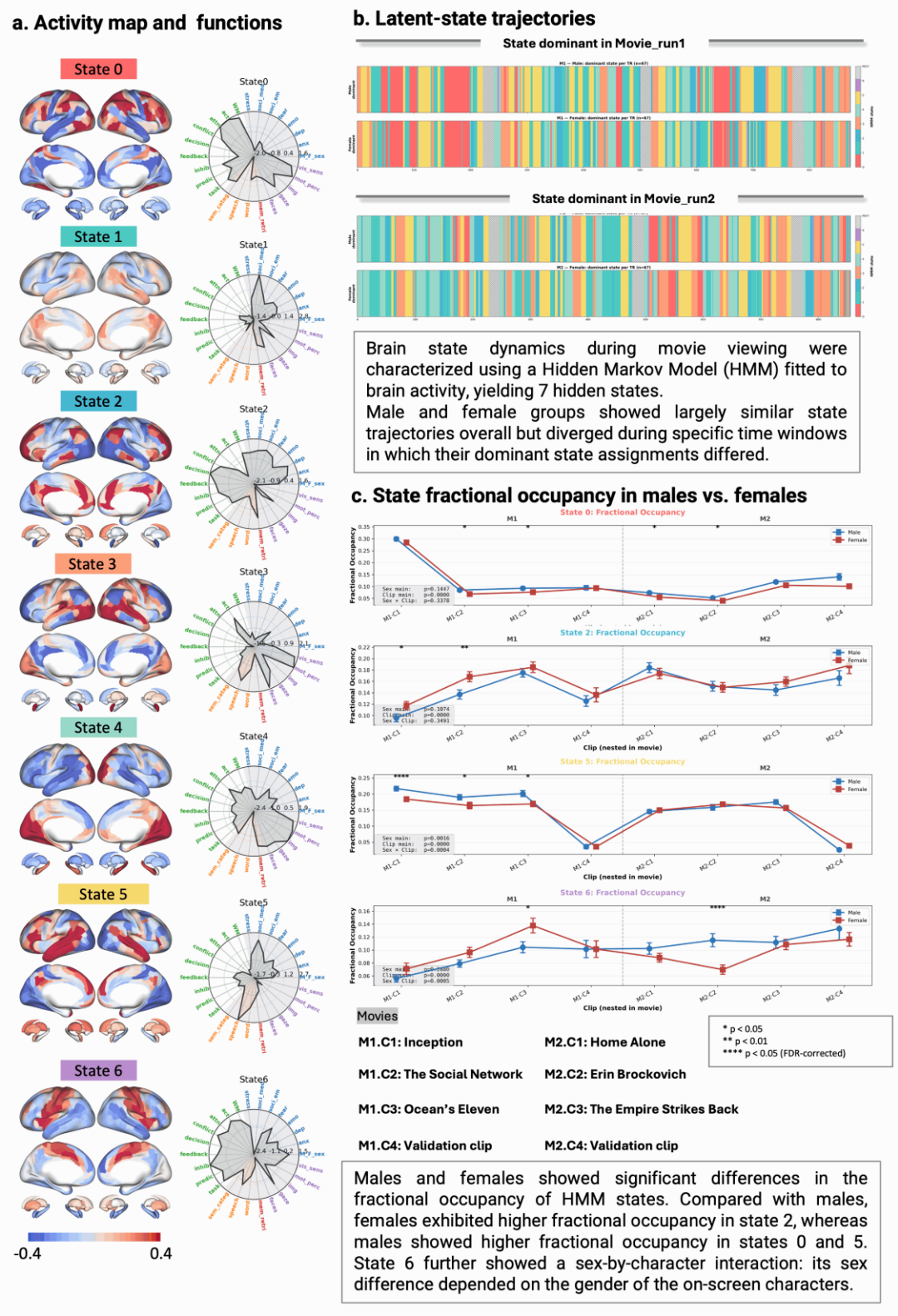
Topic: I.06. Social Cognition

Support: GR0402028

Title: Sex differences in latent neural states during naturalistic movie viewing

Authors: *X. WEI[1,2], J. M. GIRARD[3], J. T. BAKER[1,2], E. LIEBENTHAL[1,2];
[1]Harvard medical school, Mclean Hosp., Belmont, MA; [2]Mass Gen. Brigham Dept. of Psychiatry, Boston, MA; [3]Psychology, Univ. of Kansas, Lawrence, KS

Abstract: Converging structural and functional MRI evidence suggests sex-linked differences in the organization of brain networks (Ritchie et al., 2018). However, how sex differences in brain-state dynamics during real-world perception remains unclear. Here, we analyzed 7T Human Connectome Project fMRI data from two independent runs of movie viewing (four clips per run, each 3-4 min long) using a Hidden Markov Model (HMM; Vidaurre et al., 2017) in healthy, age-matched males and females (n=67 each). An HMM fitted to the whole-brain time series of 374 regions of interest yielded 7 recurring brain states. Each was functionally interpreted by reverse inference (Yarkoni et al., 2011) and linked to per-second social-visual, speech, and emotion-valence features from movie via brain encoding (Naselaris et al., 2011). We quantified each state's fractional occupancy (FO) in each clip and tested sex effects with mixed-effects models. Males and females showed largely overlapping latent-state trajectories, but differences emerged in specific states and stimulus moments(Figure 1). Females showed higher FO in state 2 ($p < 0.01$), associated with decision, conflict, and social emotion. In contrast, males showed higher FO in state 0 ($p < 0.05$), associated with visual-sensorimotor, attention, and working memory, and state 5 ($p < 0.001$), associated with speech and social processing. State 6 (associated with cognitive control) further showed a content-dependent sex difference: females had higher FO in male-character-dominated clips but lower FO when female-character screen time was greater ($p < 0.05$). Encoding showed state 5 was driven mainly by speech, with an added social-visual contribution (added $R^2 = 0.17$ and 0.07; total $R^2 = 0.20$); accordingly, sex differences in state 5 were most pronounced when these speech- and social-visual features were strong (circular-shift permutation, FDR-corrected $p < 0.05$). Together, sex differences in latent neural-state dynamics during naturalistic viewing are temporally specific and shaped by the unfolding dialogue and social-emotional content of the stimulus.



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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Center for Cognitive Aging and Memory Clinical Translational Research Student Travel Grant

Title: Eye See Your Intentions: Adult Lifespan Differences in Motivational Cue Perception

Authors: *T. AYUB BARRES, N. C. EBNER;
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Abstract: Successful social interaction depends on regulating one's approach and avoidance tendencies as well as accurately understanding those motivations in others. Direct eye gaze signals approach while averted eye gaze signals avoidance. Inferring these motivational cues, however, may be impaired among older compared to young adults, given age-related shifts toward enhanced salience of positive while reduced sensitivity to negative stimuli, with impacts on attributions of trustworthiness. This study for the first time (i) investigated age-related challenges in perception of gaze aversion in a set of newly-modified naturalistic face stimuli from the FACES Lifespan Database that varied in gaze aversion angles and emotions; and (ii) tested effects of gaze aversion perception on trustworthiness attributions in adults aged 18 to 88 years. Participants (N = 221; recruited via Prolific) rated a large set of faces regarding both gaze aversion and trustworthiness. Greater gaze aversion angle was associated with greater perceived gaze aversion, with this effect less pronounced with older age. Further, less perception of gaze aversion was associated with greater trustworthiness attributions, and again especially with older age. These results suggest age-related challenges in perception of gaze aversion, which signal approach/avoidance motivations, and could underlie greater exploitation risk in aging, as reduced perception of gaze aversion was associated with greater trustworthiness attributions. Beyond advancing understanding of perceptual-motivational accounts in aging, this work also extends the FACES Lifespan Database corpus by making the gaze-modified face stimuli and their accompanying norm ratings publicly available for research use.

Disclosures: T. Ayub Barres: None. **N.C. Ebner:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.10/HH11

Topic: I.06. Social Cognition

Support: the Brain Science and Brain-like Intelligence Technology National Science and Technology Major Project of China (grant no. 2022ZD02051030, to S.-G.K.)
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Title: Contextual Modulation of Social Interaction Perception in Scene-Selective and Social-Cognitive Brain Regions

Authors: *C.-Y. TIAN[1], S. KUAI[2,3,4];
[1]East China Normal Univ., Shanghai, China; [2]The Sch. of Psychology and Cognitive Sci., East China Normal University, China; [3]NYU-ECNU Inst. of Brain and Cognitive Science, New York Univ. Shanghai, Shanghai, China; [4]Shanghai Ctr. for Brain Sci. and Brain-Inspired Technol., Shanghai, China

Abstract: Human perception of social interaction is not solely based on the actions and relationships of interacting individuals but is strongly influenced by the scenes in which interactions occur. Social scenes provide information about spatial layout, object configuration, and environmental constraints, while also activating knowledge about whether an interaction is common, socially appropriate, and physically plausible in a given context. Here, we combined behavioral and neuroimaging experiments to investigate how scene context shapes social interaction perception and its neural representations. Behavioral results showed that judgments of the same social interaction varied across scenes along three dimensions: occurrence frequency, social normativity, and physical plausibility. Occurrence frequency was the strongest predictor of interaction judgments, followed by social normativity and physical plausibility. Neuroimaging results revealed distinct neural representations of scene-dependent social interaction information. The early visual cortex primarily represented low-level visual features, whereas the higher-level visual and social-cognitive regions encoded abstract scene-interaction relationships. The occipital place area (OPA), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS), and middle temporal visual area (MT) encoded information about occurrence frequency; OPA, TPJ, and pSTS additionally encoded social normativity. These findings demonstrate that social interaction perception depends on contextual scene information and suggest that scene-selective and social-cognitive regions jointly integrate perceptual input with contextual and social knowledge during social interaction perception.

Disclosures: C. Tian: None. **S. Kuai:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

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Program #/Poster #: PSTR110.11/HH12

Topic: I.06. Social Cognition

Support: Basic Science Research Program (RS-2024-00459828) through NRF of Korea
Creative-Pioneering Researchers Program through Seoul National University
Frontier Fellowship through Seoul National University

Title: From Cortical Social Dimensions to Hippocampal Relational Representations

Authors: *W. KANG[1,2], M. KWON[1,2], S.-H. LEE[1,2];
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Abstract: Social relationship recognition requires the integration of multiple dimensions of social information into coherent relational representations. In our previous work, we identified two principal dimensions underlying interpersonal relationship recognition: Amity-Hostility (PC1) and Restrained Amity-Suppressive Hostility (PC2). These dimensions are processed in distinct cortical systems, with PC1 primarily represented in the right posterior superior temporal sulcus (rpSTS), and PC2 in the right ventromedial prefrontal cortex (rvmPFC), indicating a distributed and modular organization of social relationship information processing. However, the neural mechanisms by which these dimension-specific cortical representations are integrated into unified relational representations that support social recognition remain poorly understood. In the present study, we investigated whether and how the hippocampus integrates these distinct cortical social dimensions during social relationship recognition. Using event-related functional magnetic resonance imaging (fMRI) data from our previous study, in which participants evaluated social relationships while viewing naturalistic movie clips, we found that dimension-specific cortical information converged in the hippocampus and was reorganized into a relational representational format. Specifically, hippocampal activity could not be explained by a simple combination of PC1 and PC2 information, indicating that hippocampal representations are not a direct reflection of cortical social dimensions. Critically, hippocampal representations were best characterized by a flexible integration model in which the relative contribution of each social dimension varied according to relational context. Collectively, these results suggest that the hippocampus integrates and reorganizes distributed cortical social information into unified relational representations that support social relationship recognition.

Disclosures: W. Kang: None. **M. Kwon:** None. **S. Lee:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.12/HH13

Topic: I.06. Social Cognition

Support: SAIL Fund, National Institute of Information and Communications Technology (NICT)

Title: Distinct neural substrates underlying facial naturalness perception and implicit discrimination between AI-generated and real faces

Authors: *J. WANG[1,2], S. NISHIDA[1,2,3,4];
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Abstract: Recent generative models can produce highly naturalistic human faces that are often mistaken for real ones. Indeed, previous behavioral studies have shown that people fail to explicitly distinguish AI-generated faces from real ones.Nevertheless, a previous study suggests that the brain implicitly discriminates between AI-generated and real faces even when explicit judgments fail (Moshel, 2022). However, little is known about the neural substrates underlying such implicit discrimination and how they relate to the neural substrates for explicit judgments of facial authenticity. To address these questions, we collected fMRI data from 74 participants while they viewed AI-generated and real facial images and rated the naturalness of each face. Behavioral results revealed that participants judged AI-generated faces as more natural than real faces, indicating that explicit perceptions of facial naturalness did not accurately reflect facial authenticity. Whole-brain GLM analyses showed that explicit perceptions of facial naturalness were signaled in widespread brain regions, particularly frontal pole, posterior cingulate cortex and precuneus. More importantly, despite the lack of behavioral evidence distinguishing AI-generated from real faces, these two face types were differentially represented by neural activity in a separate set of regions, including posterior visual and posterior medial regions such as the precuneus and posterior cingulate cortex. This differentiation remained largely unchanged in an additional analysis in which subjective naturalness ratings were matched between AI-generated and real faces. These results suggest that the neural substrates underlying the implicit discrimination between AI-generated and real faces are largely distinct from those underlying explicit perceptions of facial naturalness. Our findings provide important insights into the neural mechanisms underlying the implicit processing of AI-generated information. Furthermore, these insights may contribute to improving human ability to detect AI-generated information by developing training methods that bring such implicit neural processing into conscious awareness.

Disclosures: J. Wang: None. **S. Nishida:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.13/HH14

Topic: H.03. Motivation

Title: Empathy Profiles and Structural Brain Segmentation in Adults

Authors: *S. ARROYO[1], F. A. BARRIOS[2], S. ALCAUTER[3], D. ATILANO-BARBOSA[4], J. ESQUIVIAS[2];
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Abstract: Empathy is essential to our daily lives, enabling deep connections and compassionate responses. It is a key domain of social cognition for forming and maintaining relationships (Coundouris et al, 2020) and is defined as the ability to infer and share emotional experiences (Schmidt et al., 2017). The Interpersonal Reactivity Index (IRI) measures empathy via four self-report subscales: Perspective Taking (PT) and Fantasy (FS), which assess cognitive empathy (the spontaneous attempt to understand another's viewpoint and the capacity to imagine oneself in fictional situations, respectively); and affective empathy with Empathic Concern (EC) and Personal Distress (PD), EC measures feelings of compassion, concern, and caring in response to others' distress and PD assesses the feelings of anxiety and distress when observing another's negative experiences.
In this study, 107 young adults (62 women) aged 18-30 completed the IRI and underwent T1-weighted structural MRI acquisition. We examined gender differences, age-related trends and explored potential neuroanatomical associations. Women scored significantly higher than men on EC (pFDR=0.0132), PD (p=0.0132) and affective empathy (pFDR=0.0022). Within this restricted age range, no significant age-IRI associations were found. To explore potential neuroanatomical associations with continuous IRI dimensions, structural segmentation measures were analyzed using generalized linear models. A permutation test was used for statistical inference and showed associations between IRI dimensions and regions. Cognitive empathy was associated with hippocampal, putamen, orbitofrontal, middle temporal, precuneus and occipital pole measures; affective empathy with putamen, left parietal and anterior insula measures. Among subscales, PT was linked to cerebellar, hippocampal, orbitofrontal, temporal, supramarginal and entorhinal regions; FS to putamen, parietal, precuneus and occipital pole; EC to hippocampal, putamen, calcarine and anterior insula measures; and PD to basal forebrain, putamen, superior frontal and postcentral regions. These effects did not survive multiple-comparison correction.
In conclusion, women showed higher scores in affective empathy in this young adult sample, whereas age-related effects were not significant. Structural brain segmentation showed associations between IRI dimensions and empathy-related regions. These candidate structures will be further examined using voxel-based morphometry to determine whether empathy profiles are associated with localized structural brain differences.

Disclosures: S. Arroyo: None. **F.A. Barrios:** A. Employment/Salary (full or part-time):; Principal Investigator. **S. Alcauter:** A. Employment/Salary (full or part-time):; Principal Investigator. **D. Atilano-Barbosa:** None. **J. Esquivias:** None.

Poster

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Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.14/HH15

Topic: I.06. Social Cognition

Support: NIMH Intramural Research Program
Australian Research Council FT200100843

Title: What's in a face and when: Unveiling the timecourse of naturalistic face perception

Authors: *S. JAPEE[1], L. KELEMEN[1], N. SIMMONDS[1], L. TEICHMANN[2], J. TAUBERT[3], C. I. BAKER[1];
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Abstract: We encounter a multitude of faces in our daily lives, each conveying vital information for social interactions. For example, facial information such as identity, age, gender, race, and emotional expression, convey important social signals that helps us know who a person is, how they are feeling and their behavioral intentions. While prior research has focused on identifying the brain regions that are involved in processing these different facial signals, less is known about the temporal dynamics with which these distinct signals emerge. Further, many studies have relied on highly controlled photographs of faces that fail to capture the heterogeneity of faces and expressions we encounter in daily life. To address these limitations, here we collected magnetoencephalography (MEG) data while participants (n = 20) viewed naturalistic face images from the Wild Faces Database (WFD) - a large collection of face images with heterogeneous facial features, identities and expressions. In a separate behavioral experiment, participants completed an odd-one-out triplet task using these same images. Analysis of these behavioral judgements revealed 15 distinct dimensions of facial information reflecting a combination of perceptual and inferred features such as age, gender, race and emotional expression. We examined the temporal profiles of brain activity elicited by these behaviorally-derived dimensions using time-resolved analysis of the MEG data. We found that nearly all the latent dimensions showed a reliable time-locked relationship with MEG activity, although the strength and timing of the effect varied substantially across dimensions; with some dimensions being associated with early transient effects in the MEG data while others showed delayed yet sustained effects. Further analyses of these data will shed light on exactly when different facial signals are extracted during neural processing. By combining naturalistic stimuli, behavioral modeling, and time-resolved neuroimaging, this work provides new insights into the temporal dynamics of facial information processing under more ecologically valid conditions.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.15/HH16

Topic: I.06. Social Cognition

Title: Cerebellar Contributions to Socio-Affective Prediction Errors

Authors: *N. SERINO[1], L. HOFFMAN[1], M. CALLINAN[1], S. MARTINEZ[1], C. HELION[1], V. P. MURTY[2], I. R. OLSON[1];
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Abstract: Growing evidence suggests the cerebellum (Cb) plays a meaningful role in social and affective processing, beyond its well-established contributions to motor functions. Due to its highly uniform cytoarchitecture, the Cb might employ a common computational mechanism across functional domains. In the motor domain, the Cb engages in supervised learning to fine-tune behavior through prediction error (PE) computations. We propose that a similar algorithm supports its role in social and affective processes. To investigate Cb PEs in the socio-affective domain, we developed a novel emotion induction task as an extension of canonical faux pas paradigms by using embarrassment as a model of socio-affective PE. This task consists of two sessions. In the first session, participants (N = 19) were recorded performing a series of embarrassing tasks designed to induce a social PE (e.g., singing or dancing) and control tasks not meant to induce PEs (e.g., sitting at a computer). One week later, during fMRI scanning, participants unexpectedly viewed recordings of both themselves and a paired partner, rating how they felt about each performance and how they expected others to evaluate it. Behaviorally, participants demonstrated PEs during the embarrassing but not the control conditions, such that participants consistently underestimated how positively their partner would rate them ($p < .05$). This reflects a discrepancy between expected and actual outcomes. Further, mass univariate analyses of the neuroimaging data revealed activation in Cb lobules crus I/II when contrasting embarrassing versus control conditions (cluster-corrected: $Z > 3.1$, $p < .05$). We also observed activation in cortical and subcortical regions previously associated with embarrassment, including the frontal operculum, anterior insula, and amygdala. These findings align with a growing body of work implicating crus I/II in social cognition and provide preliminary support for the cerebellum's role in socio-affective PE processing, laying the groundwork for future analyses examining how the Cb communicates with upstream regions during social and affective processing.

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Poster

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Topic: I.06. Social Cognition

Support: DIP grant SH 752/2-1
DIP grant GR 3619/19-1

Title: Loneliness shapes both sides of interaction: Neural and Hormonal Dynamics During Social Interaction

Authors: *D. SHAMAI-LESHEM[1], Y. MOLCHO FISCHER[1], Y. AVNOR[1], V. GRINEVICH[2], S. WAGNER[3], R. HURLEMANN[4], S. G. SHAMAY-TSOORY[3];
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Abstract: Loneliness is a major risk factor for mental and physical health. Typically understood as a subjective experience, its consequences may extend to those who interact with a lonely partner. Here, we reframed loneliness as an interpersonal condition and tested whether the presence of lonely individuals alters affiliative biological mechanisms in both interaction partners. Using hyperscanning fNIRS and oxytocin (OT) measurements during real-life social interactions, we compared dyads of two low-loneliness individuals (LL-LL; n = 34 dyads), or one high-loneliness and one low-loneliness individual (HL-LL; n = 37 dyads). Seventy-one same-gender dyads (N = 142 participants; 66.4% female; Mage = 24.18 years, SD = 4.00) meeting for the first time participated in a five-minute unstructured conversation while undergoing dual-fNIRS hyperscanning. Salivary OT, mood, and social-affiliative measures were assessed before and after the interaction. Inter-brain synchrony (IBS) was quantified using wavelet transform coherence across bilateral inferior frontal gyrus, premotor, and dorsolateral prefrontal regions. Results show that HL participants reported greater anticipatory anxiety before the interaction relative to LL participants. At the hormonal level, oxytocin responses differed as a function of partner loneliness. OT increased in HL participants and in LL participants paired with another LL participant, whereas LL participants interacting with an HL partner showed no significant OT increase (p = .03). At the dyadic level, HL-LL dyads exhibited significantly lower IBS in the left premotor cortex compared with LL-LL dyads (p = .004). Furthermore, partner loneliness predicted reduced salivary OT, which in turn predicted reduced subjective bonding, yielding a significant indirect effect. Despite heightened anxiety and negative affect before the interaction, HL participants reported similar post-interaction enjoyment and bonding compared with LL participants. These findings provide the first direct evidence that loneliness shapes social encounters in both interaction partners at the hormonal, neural, and behavioral levels. This opens new directions for interventions, which not only target the cognitive or emotional patterns

of the lonely individual, but also the dyadic processes through which those patterns undermine connection.

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Poster

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Program #/Poster #: PSTR110.17/HH18

Topic: I.06. Social Cognition

Support: W911NF-26-2-A019

Title: Inter-brain complexity synchronization as a novel approach to track coordination in human teams

Authors: *J. C. BRADFORD[1], S. SULLIVAN[2], K. MAHMOODI[2], S. KERICK[2], D. L. BOOTHE[2], B. STORY[2];
[1]US Army DEVCOM, US Army Res. Lab., Bel Air, MD; [2]US Army DEVCOM, US Army Res. Lab., APG, MD

Abstract: Complexity Synchronization (CS) captures coordination and information flow between systems by tracking how their complexity co-varies over time. While CS has been observed within individuals across organ networks, it has not been applied between individuals [1]. We introduce a novel application of CS to capture inter-brain dynamics during teaming. Unlike hyperscanning metrics influenced by shared stimuli or stationarity assumptions, CS analyzes signal complexity and detects coordinated fluctuations in scale-free dynamics. We measured the neural activity of dyads performing a complex, real-world task. We hypothesized that inter-brain CS emerges during teaming and its magnitude is related to performance. Seventeen healthy subjects paired in dyads completed a resting baseline, active listening control, and three rhythmic tasks: synchronized clapping and two instrumental tasks (performing familiar and unfamiliar musical arrangements). We recorded and synchronized 64-channel EEG and audio during each condition. Inter-brain CS was computed by correlating partners' scaling-index temporal trajectories δ(t) derived via Modified Diffusion Entropy Analysis (MDEA) with a 9.6s moving window sampled every 2.4s. Questionnaires assessed individual experience, partnership history, and familiarity with paired partner; trial-level rhythmic errors were computed as the average temporal differences between note onsets. Significant inter-brain CS emerged during interactive rhythmic tasks, but not during passive conditions of listening or rest. We did not find a significant relationship between interbrain CS and rhythmic error for either the clapping or musical performance conditions. We found a significant relationship between inter-brain CS and

the degree of familiarity between subjects. This study introduces the first use of CS to track teaming via neural signals. Our analysis suggests that CS is sensitive to active coordination rather than shared stimuli. The relationship between familiarity and CS suggests that prior relational history contributes to neural coupling. Together, these findings indicate that CS should be further explored as a technique for measuring coordination in teams. [1] Schizas, I., Sullivan, S., Kerick, S., Mahmoodi, K., Cortney Bradford, J., Boothe, D. L., ... & West, B. J. (2025). Complexity synchronization analysis of neurophysiological data: Theory and methods. Frontiers in Network Physiology, 5, 1570530.

Disclosures: J.C. Bradford: None. **S. Sullivan:** None. **K. Mahmoodi:** None. **S. Kerick:** None. **D.L. Boothe:** None. **B. Story:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.18/HH19

Topic: I.06. Social Cognition

Support: DARPA contract #HR001124C0497 as part of the Objective Prediction of Team Effectiveness via Models of Performance Outcomes (OP TEMPO) program

Title: Role-Specific Neural Coordination and Autonomic Regulation Predict Performance in Operational Teams

Authors: *J. SUSSMAN-FORT[1], J. CRAIGHEAD[2], D. WILSON[2], S. KLINE[3], T. HILSABECK[2], N. PETROFF[3], J. COHN[2], D. SCHMORROW[2], J. FOLSOM-KOVARIK[2], A. WOODS[2], B. T. STONE[2], E. SALAS[4], L. BERGER[6], M. KHALID[5], R. LINHARDT[5], A. WEST[5], C. BERKA[7], E. THUNEN[7], S. DODEL[8];
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Abstract: Assessing operational readiness is essential for building effective military teams. While individuals and units typically progress through standardized training prior to mission execution, predicting team-level performance such that it translates to a readiness determination remains a challenge. The goal of this study is to identify and characterize objective biomarkers for team performance prediction. We present our results based on two data collection events from a five-member Marine Fire Support Teams (FiSTs) engaged in a simulation-based training environment. We ground our approach in *Team Behavioral Competency Theory (TBCT)*, which is defined by Leadership, Mutual Performance Monitoring, Back-up behavior, Team Orientation, and Adaptability and has been empirically tested across military, aviation, and healthcare settings. We map this framework to mission specific behavioral windows and for each individual

FiST member we measure electroencephalography (EEG), heart rate (HR), and audio/video. We characterize these multimodal signals at the individual and team level, modeling team structure as an organized system in which members occupy distinct functional roles, with performance emerging from how effectively these roles synchronize, coordinate, and differentiate under task demands. Our results output a set of features to populate the edges of a causal model. Selected model features were primarily neural, capturing role-specific cognitive dynamics and team/dyadic coordination, with HR measures providing a complementary physiological-state layer reflecting arousal, workload, and autonomic regulation. For n=36 missions, across 8 FiSTs we can predict ground truth subjective marine instructor ratings at the overall mission and subtask level (accuracy > 80%). Our results suggest that changes in role-based and neural synchronization features across the team during key mission behavioral windows exist as structured relationships supporting a causal hypothesis for predicting team performance. By applying TBCT we bridge the gap between operational team behaviors and measurable biomarkers laying the foundation for application to other small, rapidly composed teams.

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Poster

PSTR110: Neural Mechanisms of Human Social Cognition

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Program #/Poster #: PSTR110.19/HH20

Topic: I.06. Social Cognition

Support: W911NF-26-1-A101

Title: Investigating interbrain synchrony across fNIRS channels during three-person teams' search-and-rescue performance

Authors: *U. DUBEY, A. NECAISE, J. AN, Y. HASHEM POUR, L. FAVELA, M. AMON; Indiana Univ., Bloomington, IN

Abstract: Investigations of interbrain synchrony during social interactions are often limited to examining the brain activity of dyads. However, less is known about patterns of high-order synchrony in groups of three or more. The current study applies recurrence quantification analysis (RQA) to measure across 9 channels of functional near-infrared spectroscopy (fNIRS) in teams of three according to their joint recurrence rate (jRR). The advantage of estimating interbrain synchrony using jRR the ability to scale the analysis to include many channels and participants while still being able to identify the individual channels that contribute to apparent high-order associative structures. Our objective was to explore whether three-way interbrain

synchrony could be detected using the jRR during task-oriented behavior, and we examined whether these high-order estimates were related to team outcomes. Data from 9-teams of 3 was retrieved from the Theory of Mind-based Cognitive Architecture for Teams (ToMCAT) dataset. Teams were selected based on the availability of valid data after alignment across team members. Each team completed an approximately 17-minute Minecraft search-and-rescue task in which they worked together to remove collapsed rubble from a damaged building, located trapped victims, and extracted victims from the environment. These tasks required coordination to complete, and teams received a higher score based on the number of completed tasks. After excluding invalid recordings and down sampling to 1hz, fNIRS channels were selected from source-detector pairs positioned over the frontopolar and prefrontal cortex (FP1, FPz, FP2, AF7, AF3, AFz, AF4, AF8). Recurrence plots (RPs) were generated from the timeseries of individual channels, and the jRR across participants was taken as the element-wise sum of their corresponding RPs. In comparison to an artificial baseline with scrambled teams, we found evidence of significant three-way interbrain synchrony in the AFz-AF4 source detector pair, $t(11.59) = 2.92$, $p = .01$, $d = 0.85$. Furthermore, joint recurrences between team members in AFz-AF4 were three-times more likely than chance to occur simultaneously with joint recurrences in the AF3-AFz and AFz-FPz channels. In comparison to behavioral outcomes, there appeared to be a positive correlation between overall jRR and task scores, but this correlation did not meet the threshold for significance, $r = 0.44$, 95% CI [-0.32, 0.85], $p = .25$. Although a small-n exploratory study, our results contribute to the hyperscanning literature, supporting joint RQA as a valid approach to assessing high-order synchrony in groups larger than two and with many channels.

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Poster

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Program #/Poster #: PSTR110.20/HH21

Topic: I.06. Social Cognition

Title: Inter-Brain Coherences from The Triad-fMRI Hyperscanning: A Public-Good Game Experiment

Authors: *C. YANG[1], M.-H. WENG[2], D.-Y. CHEN[3], C.-C. KUNG[3], Y.-P. CHEN[4]; [2]Dept. of Econ., [3]Dept. of Psychology, [1]Natl. Cheng Kung Univ., Tainan, Taiwan; [4]Dept. of Intl. Business, Natl. Taiwan Univ., Da'an District, Taipei City, Taiwan

Abstract: Recent neuroscience research on social interaction has increasingly adopted hyperscanning in dual-scanning designs. Despite the complexity of human social behavior, investigating neural coordination among multiple participants is essential for understanding real-life interactions.

With a 2x2 (cooperation threshold x reward design) public good game experiment, we analyzed the fMRI hyperscanning data from 45 valid triads (of 135 participants; 5 triads were excluded due to data quality issues) through the Fourier Transform Coherence (FTC) method to reveal the implicit coordination in neural synchrony when in the "feedback" phase, in which the outcome was revealed. The analysis focused on the asymmetric reward condition, with trial outcomes matching expectations from rational game-theoretic equilibria. Coherence values among dyadic pairs within each triad (AB, BC, CA) were averaged to ensure bidirectional correspondence between ROI regions. Based on the research interest, seeds were set in the left inferior parietal lobule (l-IPL, self-interest-related) for whole-brain analysis at a task-specific frequency of 0.0417 Hz (1/24s, corresponding to the average trial duration).
In the FTC results, we found that when using the l-IPL as the seed, a cluster within the r-IPL (101 voxels, centered at [66, -24, 24]) was identified with the second peak coherence value at the expected .0417 Hz across all three dyadic pairs (AB/BC/AC). Based on the known role of IPL in self-interested decision-making, synchrony within triads may reflect the rational decision-making characteristic of the selected analytic condition, supporting its common role in multiperson interactions.
In conclusion, the neural results imply that under conditions aligned with game-theoretic rationality, the self-interested computation dominates the cognitive process. To sum, these findings reveal inter-subject neural synchrony within the triad, demonstrating the utility of triad-hyperscanning in advancing understanding of social cognition.

Disclosures: C. Yang: None. **M. Weng:** None. **D. Chen:** None. **C. Kung:** None. **Y. Chen:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.21/HH22

Topic: I.06. Social Cognition

Support: NSTC-114-2410-H-006-002

Title: Challenges and workarounds in Inter-brain coherences from fMRI hyperscanning: the public-good game example

Authors: *C.-C. KUNG[1], C.-H. YANG[2], M.-H. WENG[3], D.-Y. CHEN[4], Y.-P. CHEN[5]; [2]The Cross Col. Elite Prog., [3]Econ., [1]Natl. Cheng Kung Univ., Tainan, Taiwan; [4]Dept Psychology, Natl. Cheng Kung Univ., Tainan, Taiwan; [5]Intl. Business, Natl. Taiwan Univ., Taipei, Taiwan

Abstract: While fMRI hyperscanning has been gradually used to explore various social phenomena, pushing social neuroscience to a new level, unconstrained data analysis methods also reveal one of its challenges: due to the scan time limit (usually 1.5 hours), the number of

available trials for candidate conditions is often insufficient. For example, in the public good game, the percentage of all-voted-yes trials was typically < 10%, limiting the applicability of frequency-based coherence analyses, which typically require >300 time points. The current 4-person public good game experiment (see Fig. 1), which included triads fMRI (N=135) and another behavioral test (N=45), aims to illustrate this limited-trial problem and propose one solution. By varying the triad groups and the number of concatenated trials: [5 45],[7 32], [9 25], and [14 16], we found that within a certain range, the coherence peaks were relatively consistent: in this case, higher inter-personal coherence between two l-IPLs) of the same pairs than those from the permuted pairs (Fig. 2). In addition, to evaluate the effect of trial order, the orderly concatenated trial units (following correct trial histories) vs. shuffled-order trials were compared, and the mean peak coherence histograms did not differ significantly. Together, these results support the claim that, under reasonable constraints, concatenating trial betas across subjects may be a feasible solution to the problem of insufficient trial counts in fMRI hyperscanning coherence analyses.

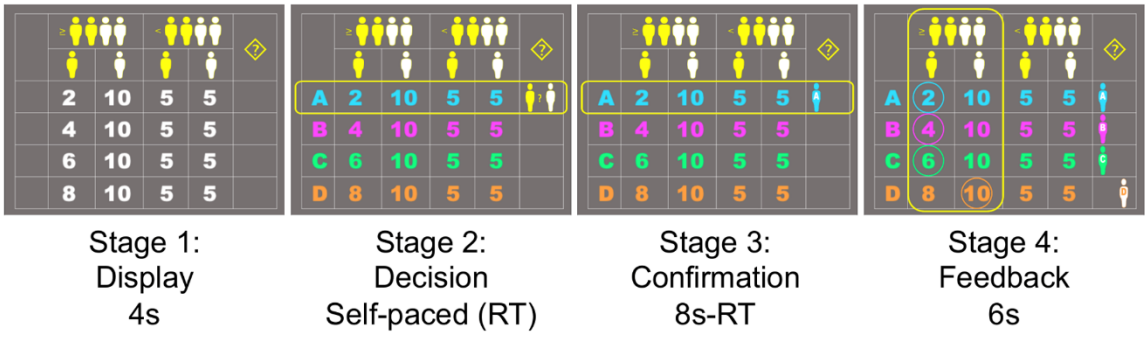


Fig. 1 triad-fMRI hyperscanning public-good game exp design

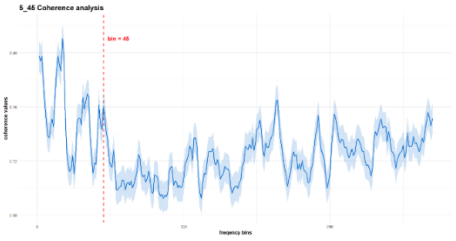


Fig. 2 (a) 5_45: pair only

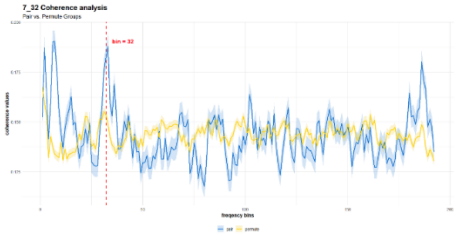


Fig. 2(b) 7_32: pair v.s. permuted

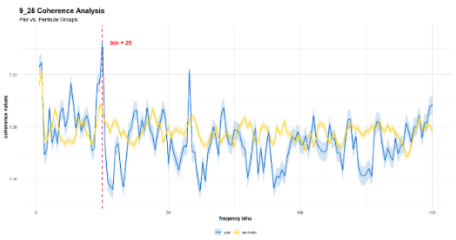


Fig. 2(c) 9_25: pair v.s. permuted

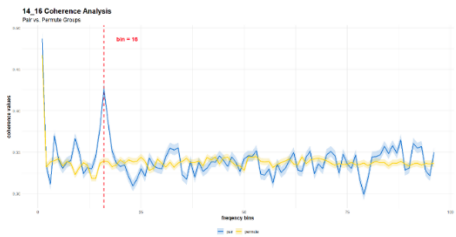


Fig. 2(d) 14_16: pair v.s. permuted

Disclosures: C. Kung: None. **C. Yang:** None. **M. Weng:** None. **D. Chen:** None. **Y. Chen:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.22/HH23

Topic: I.06. Social Cognition

Title: Effects of Perceived Social Support on Prosocial Behavior in Prospective Memory Tasks

Authors: *N. TAHERBHOY[1], N. ARORA[1], T. BERMAN[1], S. A. RASKIN[2];
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Abstract: Prospective memory (PM), the ability to remember future intentions, is an important cognitive function that is used in daily, independent living. Prosocial behavior and perceived social support may positively impact PM recall through social and motivational framing. Though this combined relationship has not been fully researched, prosocial behavior does increase prospective memory recall when social importance is attached to carrying out a task. A sample of 31 Trinity College students, ranging in ages from 18 to 22, having English fluency, and lacking any diagnosed neurological or psychological illness, were recruited and randomly assigned to a comparison group and an experimental, prosocial group. Participants were tested with the Memory for Intention Screening Test—Short Form (MIST-S), the Multidimensional Scale of Perceived Social Support (MSPSS), and the Comprehensive Assessment of Prospective Memory (CAPM). Towards the start of the MIST-S, both groups were asked to sign their initials on the last page of the CAPM upon its completion. The comparison group was instructed that signing was necessary to keep the materials organized, and the experimental group was instructed that signing was needed to help a lab member successfully complete her thesis. Results demonstrated that there were no significant differences noted between the groups on the CAPM, the MIST, MSPSS, years of education or age. However, the comparison group scored significantly higher on verbal response on the MIST ($t(29)=-2.091$, $p=0.045$), whereas the prosocial group scored significantly higher on action response, ($t(15.00)=2.236$, $p=0.041$). A binary logistic regression was fitted to account for the effect of prosocial treatment and MSPSS regressed on the PM task. In the model, MSPSS was not a significant predictor, ($B=0.024$, $SE=0.049$, $Wald=0.242$, $p=0.623$, $OR=0.976$). In contrast, prosocial treatment significantly predicted PM task performance ($B=1.877$, $SE=0.830$, $Wald=5.117$, $p=0.024$, $OR=6.537$). Thus, results demonstrated that participants who were prosocially instructed were more likely to complete the PM task than those in the comparison group. The findings also suggested that prosocial behavior positively impacted PM recall, but perceived social support did not have a significant impact on the relationship between prosocial behavior and PM recall. However, the results may have been impacted by a small sample size leading to limited variability.

Disclosures: N. Taherbhoy: None. **N. Arora:** None. **T. Berman:** None. **S.A. Raskin:** A. Employment/Salary (full or part-time):; Trinity College.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.23/Web Only

Topic: I.06. Social Cognition

Title: Human Personality Forms a Small World: Different in Males and Females

Authors: *H. SHAHI[1], A. GHADERI[2,1];
[1]Iranian Neurowave Lab., Isfahan, Iran, Islamic Republic of; [2]Dept. of Psychology, Fac. of Social Sci., Özyegin Univ., Istanbul, Turkey

Abstract: Personality has long been a central topic in psychological research, with numerous studies mapping out how traits are structured, measured, and distributed. But here's a question that hasn't really been asked: when you look at how people in a community resemble each other in terms of personality, does the overall pattern form something like a tight-knit web? A structure in which clusters of people are highly similar within themselves, yet remain close in personality to other clusters through unexpectedly short connecting pathways. And does this web of connections take on a different shape when you trace it among males versus females? Focusing on an age range of 18 to 80 across two datasets, we split the datasets by sex and then randomly down sampled each group to a number divisible by 1,000. These were then randomly assigned into groups of exactly 1,000 individuals, yielding the following breakdowns: Johnson-300 dataset (males N=99,000, females N=148,000, 300 items questionary) and Johnson-120 dataset (males N=207,000, females N=304,000, 120 items questionary). Within each group, we calculated Spearman correlations between all individuals based on their personality questionnaire items, and then applied the small-world propensity (SWP) function to the resulting network. Finally, we ran a permutation t-test with 5,000 iterations to compare the SWP scores between the female and male groups. For the Johnson-300 dataset, the mean SWP for males was 0.6711 (SD=0.0104), while for females it was 0.7036 (SD = 0.0101), a statistically significant difference ($P<0.001$, $T=24.56$). The Johnson-120 dataset revealed similar pattern: males showed a mean of 0.7049 (SD=0.0104) and females a mean of 0.7367 (SD=0.0092), with a significant gap ($P<0.001$, $T=36.39$). The findings confirm that for both males and females, the personality network exhibits a small-world architecture (values above 0.6). These findings suggest that, like many other natural systems, human personalities may be arranged within an optimally connected space. In this space, similar personalities form clustered local communities, whereas seemingly distant personalities can still be connected through only a small number of intermediate personality profiles. Notably, the female group consistently showed a significantly higher SWP than the male group. This suggests that personality similarities within this group create clusters that either form structures with stronger internal connections, or these clusters share high similarity and strong connections with one another.

Disclosures: H. Shahi: None. **A. Ghaderi:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.24/Web Only

Topic: I.06. Social Cognition

Title: A Network-Based Typology of Personality: Detecting Sex-Specific Types with a Hierarchical Modularity Approach

Authors: *N. ABBASIAN[1], H. SHAHI[1], A. GHADERI[2,1];
[1]Iranian Neurowave Lab., Isfahan, Iran, Islamic Republic of; [2]Dept. of Psychology, Fac. of Social Sci., Özyegin Univ., Istanbul, Turkey

Abstract: Recently, there has been a growing movement in personality psychology away from variable-centered approaches and toward person-centered approaches that emphasize identifying personality types. However, existing methods in this area often rely on aggregate trait scores or dimensionality reduction techniques, which fail to capture heterogeneity in item-level responses. To address this limitation, the present study applied a novel hierarchical modularity approach to identify personality types based on responses to 200 items of the HEXACO-PI-R. Given that personality traits differ meaningfully by sex, all analyses were conducted separately for males and females.
The sample included 12,462 Australian adults (female N=6231), aged 18-66 years, who completed the HEXACO-PI-R. The network was derived from Spearman correlations between individuals, based on their responses to all 200 items. Modularity analysis was subsequently applied to determine how this network divides into subgroups. For each sex, a permutation t-test was conducted across 25 facets (FDR-corrected). Finally, machine learning classification was used to assess the discriminability of the extracted types.Our results showed that in both males and females, four distinct personality types were identified. Among males, Type 1 (n = 1,571), Type 2 (n = 1,650), Type 3 (n = 1,475), and Type 4 (n = 1,535). Among females, Type 1 (n = 928), Type 2 (n = 2,204), Type 3 (n = 910), and Type 4 (n = 2,198). The premutation comparisons showed highly significant differences between types in facets, and this pattern differed between the male and female groups. Machine learning approach showed a high classification accuracy (reaching 92.1% in the male and 92.1% in the female group). Our results first demonstrate that this hierarchical modularity-based approach can effectively handle the high-dimensional structure of personality questionnaire data (200 items), identifying distinct personality groups that exhibit clearly differentiated profiles. Furthermore, the findings indicate that although both males and females could be classified into four distinct personality groups, these clusters did not reflect equivalent personality profiles across sexes. This suggests that pooling male and female participants prior to clustering may obscure important sex-specific personality structures and reduce the sensitivity of the model to detect personality profiles that emerge uniquely within each sex.

Disclosures: N. Abbasian: None. **H. Shahi:** None. **A. Ghaderi:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.25/Web Only

Topic: I.06. Social Cognition

Title: Personality is Associated with Cerebellar Morphology in Young Adulthood, but Differently in Men and Women

Authors: *F. SHARIFI[1], M. DAVOUDI[2,4], A. GHADERI[3,5];
[1]Iranian NeuroWave Lab. (INWLAB), Tehran, Iran, Islamic Republic of; [2]Iranian NeuroWave Lab. (INWLAB), Mashhad, Iran, Islamic Republic of; [3]Iranian NeuroWave Lab. (INWLAB), Isfahan, Iran, Islamic Republic of; [4]Psychology, Univ. of Isfahan, Isfahan, Iran, Islamic Republic of; [5]Dept. of Psychology, Fac. of Social Sciences, Özyegin Univ., Istanbul, Turkey

Abstract: The cerebellum is a key neural structure involved in motor control and timing. Recent evidence suggests that it may also modulate cognitive functions, either through its role in movement and temporal processing or via more direct mechanisms that remain poorly understood. A growing body of evidence also supports the involvement of the cerebellum in social and personality-related traits. Beyond cerebellar function, several studies suggest that cerebellar morphology itself is associated with individual differences in personality. Although prior research has linked cerebellar morphology to certain personality domains, the findings remain highly heterogeneous, and the potential modulatory effects of demographic factors are largely unknown. Addressing this critical gap, to the best of our knowledge, the current study is the first to systematically investigate how the association between cerebellar volume and NEO personality traits varies across age and sex. Data for this study were obtained from the Human Connectome Project dataset (HCP S1200). After screening and excluding outliers, the final sample included 609 healthy adults (281 men, 328 women) across two age ranges: 22-25 and 30-35 years. Personality traits were assessed using the 60-item NEO Five-Factor Inventory (NEO-FFI), along with cerebellar morphometric data. Statistical analyses included Spearman correlations performed in MATLAB R2024b and corrected using the false discovery rate method (FDR; $q < 0.05$). In preliminary analyses, Openness was associated with cerebellar volume in young men (aged 22-25), and Extraversion correlated with left cerebellar gray matter in women aged 31-35 ($\rho=0.16$, $p=0.011$). After FDR correction, however, only the associations involving Openness in young men remained significant. Specifically, Openness showed significant associations with total cerebellar volume ($\rho=0.22$, $p=0.008$, $q=0.023$) and global gray matter volume ($\rho=0.24$, $p=0.004$, $q=0.023$). Our findings first suggest that the role of cerebellar morphology in personality is highly selective and does not give rise to the same personality profiles in men and women. These sex-specific associations may indicate that the cerebellum influences personality through partially distinct neural mechanisms or network interactions in men and women. Further, our findings suggest that the cerebellum may play an important role in

personality expression during early adulthood, but this influence diminishes with age, potentially reflecting the emergence of other mechanisms that become increasingly independent of the cerebellum as maturation progresses.

Disclosures: F. Sharifi: None. **M. Davoudi:** None. **A. Ghaderi:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.26/HH24

Topic: I.06. Social Cognition

Support: 1K01DA045735

Title: The role of painful facial expressions in behavioral and neural pain assessment in clinicians

Authors: *S. GIM[1], T. VAROUDAKI[2], N. KHALILKHANI[3], E. LOSIN[2];
[1]Penn State Univ., University Park, PA; [2]Penn State Univ., State College, PA; [3]Cornell Univ., Ithaca, NY

Abstract: Clinicians cannot directly access their patients' pain and infer it from observable cues, among which facial expressions are central. Yet, how facial expressions shape the judgment of clinicians remains unclear. In the study, 65 medical clinicians underwent fMRI while watching videos of mock patients experiencing experimentally induced pain and rated the intensity of their pain and the treatment they received. The behavioral results showed that clinicians' ratings were predicted by the patients' objective facial expressions based on pain facial expression score using the Facial Action Coding System and by the patients' own self-reported pain. Then, a whole-brain multilevel mediation analysis showed that clinicians' brain responses while watching the patients' videos mediated the effect of facial expressions on their ratings, with effects spanning affective and social-cognitive regions, including the amygdala, dorsomedial prefrontal cortex, and ventrolateral prefrontal cortex, together with occipitotemporal visual cortices implicated in face and body perception. In contrast, the component of patients' self-reports independent of facial expressions showed no significant neural mediator. Together, these findings suggest that the more pain a patient's face expresses, the more strongly it engages clinicians' affective and social-perceptual systems, which in turn shape their clinical judgments.

Disclosures: S. Gim: None. **T. Varoudaki:** None. **N. Khalilkhani:** None. **E. Losin:** None.

Poster

PSTR110: Neural Mechanisms of Human Social Cognition

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR110.27/Web Only

Topic: I.06. Social Cognition

Title: Modeling Social Exchange of Gut Microbiota: Network-Constrained Agent-Based Simulation of Microbiome Representativeness under gLV Dynamics

Authors: *M. ISHII;
The Univ. of Tokyo, Kamakura, Japan

Abstract: Research on the gut-brain axis has demonstrated that the gut microbiota can influence brain function and behavior through neural, endocrine, and immune pathways (Cryan et al., 2012). Recent human cohort studies have reported that social contacts, such as cohabitation, marriage, and friendships, are associated with similarities in gut microbiota and shared bacterial strains (Dill-McFarland et al., 2019; Beghini et al., 2024). However, it remains poorly understood whether individuals who are central in a social network acquire a microbiota profile close to the population average, and how this phenomenon—beyond simple mixing—affects intrapersonal microbial ecological dynamics.Here we constructed an agent-based model where human individuals are treated as agents and the relative abundances of 10 real-world gut bacterial species serve as state variables, to analyze the interaction between social exchange and intrapersonal microbiota dynamics. A generalized Lotka-Volterra (gLV) update equation provided the dynamics for the simulation. For the social structure, we utilized a Barabási-Albert network to compare three exchange mechanisms.Representativeness was evaluated through the distance between each agent's microbiota and the population average microbiota. Results of simulations suggest that while representative profiles easily emerge in pure Top-N exchange, where agents can choose partners with similar microbiota from the entire population, restricting exchange partners to immediate neighbors on a realistic social network dampens this effect.Our findings indicate that simple social contact does not mechanically homogenize the microbiota; rather, the emergence of population-level representativeness varies substantially depending on partner selection rules, network constraints, and the relative strength of intrapersonal gLV equilibria. Consequently, while social networks generate variance in exchange frequencies, Beghini-type microbiota representativeness was not clearly identified under the shared equilibrium of the new gLV model and network constraints.We discuss the implications of our results for cognitive processes affected by the brain-gut axis.

Disclosures: M. ishii: None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.01/HH25

Topic: I.08. Learning and Memory

Title: Temporal progression of complex olfactory rule-learning task and maturation of rule-learning engram

Authors: ***S. KUNDU**[1], A. KUMAR[2], I. REUVENI[3], J. SCHILLER[4], E. BARKAI[3];
[1]Australian Natl. Univ., ACT, Australia; [2]Neurosci. research centre, Charité-Universitätsmedizin Berlin, Berlin, Germany; [3]Univ. of Haifa, Haifa, Israel; [4]Technion Med. Sch., Haifa, Israel

Abstract: Mice trained in complex olfactory-discrimination task, take several days to learn the association between positive odour with reward, termed as “rule-learning”. We reveal, this rule-learning capability occurs abruptly in a “light-bulb” moment by two signatory physiological phenomena. Firstly, elevated somatic intrinsic-excitability, second, enhanced backpropagation of action potentials (BAP) along apical dendrites, by compartmentalized downregulation of Kv4.2 channels in distal dendrites and KCNQ (Kv7.2) channels in the proximal dendrites. Both of these findings are evident particularly in activity-marked principal neuron in piriform cortex of Fos2A-iCreER/TRAP2 mice, which function through expressing “cFos” as immediate early genes in active neurons. To capture the progression of rule-learning, dynamic of neuronal recruitment since the inception of training unveils the sharp decline of marked-cell density on the day of completion of task in comparison with first day of training. Co-localization study between first day of training with TRAP, verses accomplishment day of task by IHC of cFos reveals, nearly two-third of rule-memory cell ensemble neurons are activated from beginning of training. Causal relationship between enhanced intrinsic excitability and rule learning is shown by momentary silencing of these activity-marked principal neurons, using inhibitory DREADD (iDREADD). Such silencing leads to absolute loss of learnt memory, which reappears in absence of iDREADD activation. This study opens an avenue to understand the progression of rule-learning that occurs in a discrete moment and matured by establishing a dedicated congregation of neurons, perhaps named as “neuronal-ensemble” for rule-learning task.

Disclosures: S. Kundu: None. **A. Kumar:** None. **I. Reuveni:** None. **J. Schiller:** None. **E. Barkai:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.02/HH26

Topic: I.08. Learning and Memory

Support: Whitehall Foundation
Chan Zuckerberg Initiative
Research Corporation for Science Advancement

Title: Investigating the role of a cerebellar-thalamic-cortical circuit during movement timing adaptation

Authors: *Y. HUANG[1], F. NAJAFI[2];
[1]Wallace H. Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol. / Emory Univ., Atlanta, GA; [2]Sch. of Biol. Sci., Georgia Inst. of Technol., Atlanta, GA

Abstract: Temporal expectation helps animals predict incoming events and is important for learning, perception, and movement. However, how the brain builds and uses temporal expectation during behavior is still not fully understood.
We study this question using a novel movement-timing adaptation task in mice, in which mice learn to adjust the timing of their forelimb movements across blocks of trials. We focus on the cerebellar-thalamic-posterior parietal cortex pathway, which may provide an important link between cerebellar timing signals and cortical associative signals related to temporal expectation. To examine the causal relationship between neural activity and behavior, we use chemogenetics. To study pathway-specific responses during movement-timing adaptation, we record neural activity using two-photon calcium imaging and fiber photometry.
Our preliminary data indicate the involvement of the cerebellar-thalamic-posterior parietal cortex pathway in behavior, suggesting that cerebellar-cortical interactions shape how accurately animals time their movements. Together, this work will help define how a novel cerebellar-thalamic-cortical circuit supports temporal expectation and movement-timing adaptation.

Disclosures: Y. Huang: None. **F. Najafi:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.03/HH27

Topic: I.08. Learning and Memory

Title: Investigating the neural mechanisms of interleaved and blocked instruction during mathematics learning using OPM-MEG

Authors: *A. TANAMI[1], A. KATZ[2], M. TEICHER[3];
[2]Mathematics, [1]Bar Ilan Univ., Ramat Gan, Israel; [3]Gonda Brain Res. Ctr., Ramat-Gan, Israel

Abstract: Interleaved practice has consistently been associated with improved long-term retention compared with blocked practice in behavioral studies of learning. However, despite extensive educational research demonstrating the effectiveness of interleaved instruction, little is known about the neural mechanisms that underlie this advantage. The present study investigates how interleaved and blocked instruction influence neural activity during the acquisition of a novel mathematical topic. Approximately 30 male and female high-school students in grades 11-12 enrolled in advanced mathematics courses are being recruited and will be assigned to either

an interleaved or a blocked learning condition. Neural activity will be recorded continuously using a 128-channel optically pumped magnetometer magnetoencephalography (OPM-MEG) system during both instruction and practice, and learning outcomes will be assessed using immediate and delayed post-tests. Preliminary behavioral data from an ongoing pilot study support the feasibility of the experimental paradigm, and data collection is currently underway. Neural activity will be analyzed using a recently developed geometric framework for MEG signal analysis that has previously been applied to characterize neural representations of numerical concepts across different visual stimuli. These methodological advances provide an approach for characterizing learning-related neural dynamics. By integrating mathematics education research, real-time OPM-MEG recordings, and advanced mathematical approaches to signal analysis, this study aims to provide new insights into the neural processes associated with instructional design and to contribute to the emerging field of neuropedagogy.

Disclosures: A. Tanami: None. **A. Katz:** None. **M. Teicher:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.04/HH28

Topic: I.08. Learning and Memory

Support: NIMH IRP ZIAMH002736

Title: Optogenetic suppression of perirhinal cortex during second but not first presentation of images impairs visual recognition in rhesus macaques

Authors: *J. HWANG, A. MOHANTY, S. J. WATERS, B. M. BASILE, M. A. G. ELDRIDGE, E. A. MURRAY;
Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract: The perirhinal cortex (PRC) has long been implicated in recognition memory. Monkeys with PRC lesions exhibit severe impairments in recognition memory (Meunier et al., 1993, *J Neurosci*; Nemanic et al., 2004, *J Neurosci*). In addition, human fMRI and intracranial EEG studies have shown that PRC activity is associated with familiarity-based item recognition, and reductions in PRC activity covary with familiarity strength during recognition (Staresina et al., 2012, *Nat Neurosci*). However, the specific stage(s) of recognition memory that depend on PRC function remain unclear.
To address this question, we trained two rhesus monkeys (*Macaca mulatta*) on a visual running recognition task. One monkey was trained on a touchscreen version of the task and the other on a bar-release version. In both versions of the task, an image of a single object was presented in the center of the screen after a trial was initiated. The monkeys were required to report whether the image had been seen previously. Correct responses were rewarded with a sucrose pellet or fluid,

respectively. In each session, 120 images were presented twice in separate trials, once as a novel image and once as a repeated image. The intervals between novel and repeated presentations were 0, 5, 15, or 25 intervening trials.
Following training, monkeys received an excitotoxic lesion of the PRC in one hemisphere, and then received injection of a viral vector for optogenetic manipulation into PRC in the other hemisphere. The viral vector (AAV.PHPeB mDlx::ChrimsonR-dTom) expressed an excitatory opsin in interneurons, presumably resulting in suppression of pyramidal-cell activity during illumination. Optogenetic stimulation was delivered during either the initial (novel) presentation or the subsequent (repeat) presentation of an image. Custom LED arrays (Blackrock, Utah) consisting of anterior and posterior panels were implanted over the PRC, allowing independent illumination of each region. In Experiment 1, both panels were illuminated simultaneously. In Experiment 2, the anterior and posterior panels were manipulated separately. Behavior was analyzed using logistic regression with interval, stimulation condition, and their interaction as predictors.
Suppression of PRC activity during repeat but not novel image presentations impaired recognition performance in both monkeys, and the magnitude of this impairment depended on the interval between image presentations. When the anterior and posterior panels were analyzed separately, only suppression of the posterior PRC produced this effect. These findings suggest that the posterior PRC plays a critical role in familiarity-based recognition memory.

Disclosures: J. Hwang: None. **A. Mohanty:** None. **S.J. Waters:** None. **B.M. Basile:** None. **M.A.G. Eldridge:** None. **E.A. Murray:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.05/HH29

Topic: I.08. Learning and Memory

Support: CIHR Grant #452424

Title: Representational Drift in the Retrosplenial Cortex

Authors: *J. HUTCHISON[1], A. ATKINSON[1], M. H. MOHAJERANI[2], R. J. SUTHERLAND[1]; [1]Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Psychiatry, McGill Univ., Montréal, QC, Canada

Abstract: Representational drift is the continuous and slow change of neuronal representations over time. This occurs even when the behaviour of the animal and the environment remain stable throughout recording. The internal maps created in the brain are not static. This phenomenon has been observed across brain areas such as the primary visual cortex, primary somatosensory cortex, and olfactory regions. It was first characterized in the hippocampus with place cells,

which activate when an animal occupies a location in the environment. One region that has not been investigated thoroughly in this context is the retrosplenial cortex (RSC), located as a hub between the hippocampus and other parts of sensory and motor cortex. The RSC functions as a key cortical region within a neural network dedicated to spatial mapping, navigation, orientation, and memory. In this confirmatory study, we investigated whether RSC ensembles exhibit representational drift over an extended period. We record a total of 12 six-month-old Thy-GCaMP6s mice, 6 from each sex using an in vivo two-photon microscope to capture neuronal activity. For 30 consecutive days, these mice were tested behaviorally by running on a treadmill with an identical, stable tactile stimulus layout. The resulting data was examined by classifying cue and trajectory ensembles. The analyses also involved measuring reactivation strength, extracting reactivated features, and performing a Bayesian reconstruction. Data from both sexes were pooled as no significant sex difference were observed. Our results demonstrate a robust representational drift within the RSC. These findings highlight that representational drift is a phenomenon across the brain. Furthermore, the results suggest that the function of representational drift is a product of learning and memory mechanisms.

Disclosures: J. Hutchison: None. **A. Atkinson:** None. **M.H. Mohajerani:** None. **R.J. Sutherland:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.06/HH30

Topic: I.08. Learning and Memory

Support: NIMH R01 MH136013

Title: Bidirectional trends of signatures of plasticity across the medial temporal lobe in rhesus macaques

Authors: *V. VERMA[1], H. BARBAS[2];
[1]Boston Univ., Boston, MA; [2]Hlth. Sciences, and Anat. and Neurobio., Boston Univ., Brookline, MA

Abstract: Experience-dependent reshaping of neuronal circuits through plasticity-associated mechanisms is critical for signal processing and memory formation. Plasticity-driven processes often involve alterations in synaptic structure and connectivity. Structural changes are prominent in the early developmental stages where there is a surge of synapse formation. Stabilization of synapses is seen past the critical period by pruning of synapses. The changes in the strength of synapses are often studied in specific cortical and subcortical structures by the expression of plasticity-related genes, such as *cFOS*, *NPAS4*, *BDNF*, *CREB1*, and others. The cortex is a heterogeneous structure characterized by systematic variation in architecture across areas.

However, the spatial gradient of plasticity across cortical areas remains underexplored. To address this issue, we build on the principle of cortical systematic variation. Accordingly, the cortical limbic areas are the least differentiated areas, with fewer layers (agranular) compared to eulaminate areas, which have six layers. The elaboration in cortical lamination is accompanied by systematic changes in myelin content and spine density in excitatory neurons, which also reflect varying degrees of plasticity across cortical areas. Limbic areas are more plastic as compared to eulaminate areas. Laminar complexity increases along the medial-to-lateral axis of the medial temporal lobe, from the agranular entorhinal cortices found medially, to the inferior temporal cortices laterally, which have six layers. The less differentiated agranular areas should have higher expression of plasticity related markers as compared to eulaminate areas of the medial temporal lobe. Here we studied if there is a gradient of plasticity-related markers with gradual changes in laminar architecture along the medial-to-lateral inferior temporal region. Reelin, a glycoprotein, and NR2B receptors are expressed early in development, and should have higher expression in limbic areas. On the other hand, *Wisteria floribunda* agglutinin which labels the perineuronal net of parvalbumin positive neurons is abundant in eulaminate areas. Enhanced plasticity-related markers in limbic areas found medially in the inferior temporal lobe may facilitate learning, memory and emotional processes but also may render these areas more vulnerable to psychiatric diseases and disorders. Supported by grants from NIH (NIMH).

Disclosures: V. Verma: None. **H. Barbas:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.07/HH31

Topic: I.08. Learning and Memory

Title: A Fine-tuned Cellpose SAM Model Enables Automated Quantification of Immunofluorescent Markers of Neural Activity Across Multiple Brain Regions

Authors: *J. I. TERRANOVA, Y. PARK, T. COURI, G. ALEXANDER, P. KAPLAN, D. GILCHRIST, N. PATEL, S. WILLIAMS, T. STAVSKIS, M. CALIENDO, M. AHMAD, V. KAPLAN, P. PATEL, A. BLACK;
Anat., Midwestern Univ., Downers Grove, IL

Abstract: Quantification of activity-dependent neuronal populations across distinct brain regions is essential for understanding the circuit-level mechanisms underlying complex behaviors, such as the recall of an observational fear (OF) memory. Manual quantification of immediate-early genes like Arc (activity-regulated cytoskeleton-associated protein) and neuronal markers like NeuN yields highly accurate data, but remains labor-intensive, difficult to scale, and subject to inter-experimenter variability. Here, we leveraged Cellpose-SAM (Segment Anything Model) to develop a robust deep learning-based pipeline for automated segmentation of Arc-positive and

NeuN-positive cells. First, we subjected observer mice to an OF paradigm where they witnessed a demonstrator receive foot-shocks or a demonstrator in a non-shock control condition. 24 hours later, we tested mice for recall of the OF context, followed by brain tissue collection and Arc and NeuN immunofluorescence processing**.** We trained separate fine-tuned Cellpose-SAM models for the automated segmentation of Arc or NeuN using a ground truth dataset spanning multiple brain areas, including the basolateral amygdala, subregions of the dorsal hippocampus, and the medial prefrontal cortex. We evaluated model performance using 5-fold cross-validation, and assessed instance-level metrics, including average precision at an intersection-over-union threshold of 0.5 (AP50, with correct detections defined as predicted cells exhibiting ≥50% overlap with manually labeled cells) and global F1 score (defined as the harmonic mean of precision and recall). The fine-tuned Arc model achieved a per-image average AP50 of 0.73 and an average aggregate F1 score of 0.84 compared with a per-image average AP50 of 0.11 and aggregate F1 score of 0.21 obtained with the base Cellpose SAM model. Meanwhile, the NeuN model achieved a per-image average AP50 of 0.82 and an average aggregate F1 score of 0.91 compared with a per-image average AP50 of 0.60 and an average aggregate F1 score of 0.80 obtained with the base Cellpose-SAM model. Thus, the fine-tuned models demonstrated strong agreement with the ground truth annotations and improvement compared with the base Cellpose-SAM model across anatomically distinct brain regions. Together, this work establishes a scalable and reproducible framework for automated quantification of Arc-positive and NeuN-positive cells in anatomically distinct brain regions, enabling higher throughput and reducing experimenter-dependent variability in the analysis of activity-dependent neural ensembles.

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Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.08/HH32

Topic: I.08. Learning and Memory

Support: R01MH126022

Title: Experience-Dependent Formation of Predictive Sequence Representations across Mouse Dorsal Cortex

Authors: *S. TAFAZOLI, J. PARK, C. J. MACDOWELL, T. BUSCHMAN;
Princeton Univ., Princeton, NJ

Abstract: To investigate how cortical populations learn and represent temporal sequences, we performed wide-field mesoscale calcium imaging of the dorsal cortex in awake mice during

repeated exposure to structured visual stimulus sequences.
Mice were presented with sequences of visual stimuli consisting of four temporally ordered elements. Statistical regularities embedded within the sequences created learnable predictions about upcoming stimuli while balancing overall stimulus frequency across conditions. Animals were initially naïve and experienced approximately 1,500 sequence presentations per day over multiple days of training.
To quantify sequence representations, we used searchlight ROI approach to sample local population activity across the cortical surface. For each ROI, linear classifiers decoded the representation of the current stimulus, the memory of previous stimuli, and predictions about upcoming stimuli. By systematically applying this analysis across the dorsal cortex, we are mapping the spatial distribution of sensory, mnemonic, and predictive representations. Preliminary analyses suggest that these representations are dynamic and can change within a single session as animals are passively exposed to sequences.

Disclosures: S. Tafazoli: None. **J. Park:** None. **C.J. Macdowell:** None. **T. Buschman:** None.

Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.09/II1

Topic: I.08. Learning and Memory

Support: The Saban Research Institute Intramural Funding
R01MH134873
USC Neuroscience Graduate Program
Developmental Neuroscience and Neurogenetics Program
TSRI Animal Care Facility

Title: Cellular and molecular influences of in utero exposure to a High Fat High Sugar diet

Authors: *S. STACK[1], W. W. TAYLOR[1], L. KOROBKOVA[1], L. VASQUEZ[1], H. ADNEY[1], B. G. DIAS[2];
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Abstract: Fetal development is highly vulnerable to environmental insults. Increasing consumption of high-fat, high-sugar (HFHS) diets in general, and more specifically, during pregnancy is a contemporary societal challenge that significantly disrupts health of offspring. While the metabolic consequences of *in utero* exposure to HFHS are well-documented, its impact on cognitive phenotypes, such as learning and memory, remains poorly understood. We hypothesized that *in utero* exposure to HFHS induces developmental delays in learning and memory. To test this hypothesis, G0 female mice were first exposed to an acute HFHS diet for one-week prior to and then during gestation after which they were switched to a standard diet

upon giving birth. Using a discriminative contextual fear conditioning task that can be used to test the developmental cadence of forming precise memories, we find that learning and memory is delayed in G1 offspring exposed to HFHS *in utero*. Given evidence implicating the subthalamic zona incerta (ZI) in memory precision, we next characterized memory engrams in the ZI of young mice exposed to HFHS *in utero*. Notably, *in utero* exposure to HFHS altered the density of memory engrams within the ZI during memory recall compared to mice exposed to control diet *in utero*. These data suggest that prenatal HFHS exposure disrupts future functionality of cellular activity in ZI, and consequently, trajectories of learning and memory. These findings highlight how dietary insults during pregnancy can influence learning and memory during development, potentially escalating susceptibility to neurodevelopmental disorders later in life.

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Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.10/II2

Topic: I.08. Learning and Memory

Title: Focused Ultrasound Modulation of Mediodorsal and Anterior Thalamic Nuclei During Sequence Learning

Authors: *S. AHMADI NABI[1], A. DOCKUM[2], A. NEUMANN[3], A. PHIPPS[5], C. CASKEY[3], T. WOMELSDORF[4];
[1]Vanderbilt Univ., nashville, TN; [2]Vanderbilt Univ., Ashland, VA; [4]Dept. of Psychology, [3]Vanderbilt Univ., Nashville, TN; [5]Vanderbilt Univ. Inst. of Imaging Sci., Nashville, TN

Abstract: Sequence learning requires retaining the order of recent information and updating it across choices. The mediodorsal and anterior thalamic nuclei (MDT, ANT) project to prefrontal cortex and serve as bottleneck structures for cognitive control. Associative thalamic nuclei are thought to stabilize prefrontal representations and initiate updating and switching of goal representations. However, it remains unclear how MDT and ANT contribute to sequential working memory, and whether they make dissociable contributions to learning, retaining, or updating the order of visual events to guide behavior. We hypothesized that MDT and ANT support separable thalamo-frontal mechanisms for associating objects with their temporal order, updating ordinal position, and guiding future choices.To test this hypothesis, we used event-based transcranial focused ultrasound (tFUS) in two macaque monkeys performing a sequence learning task. Subjects learned through trial-and-error the serial order of multidimensional visual objects. tFUS stimulation was delivered transcranially and bilaterally using a multi-phase array transducer while subjects maintained gaze on chosen objects. During learning of different

sequences, tFUS targeted either the MDT proper or the ANT, with parts of the stimulation volume overlapping the anterior MDT; a no-sonication sham condition was used for comparison. Performance was quantified using sequence-completion rate, choice accuracy, errors per completed sequence, and repeated-sequence performance.We found that ANT sonication, but not MDT proper sonication, improved sequence learning by increasing sequence-completion rate, improving choice accuracy, and allowing subjects to complete sequences with fewer errors. When the first three sequences were repeated near the end of the session, subjects performed better during ANT sonication, suggesting improved retention or retrieval of learned sequences.These findings show that event-based tFUS can noninvasively enhance sequence-learning performance and the retrieval of learned sequence information to guide choices. Taken together, the results provide causal evidence for a role of the ANT in sequence learning and memory.

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Poster

PSTR111: Neural Circuit Mechanisms of Learning and Representation Across Species and Modalities

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR111.11/II3

Topic: I.08. Learning and Memory

Support: NIH Grant R01MH125615

Title: Neural Dynamics of Aversive Learning: Testing the Rescorla-Wagner Model with fMRI

Authors: *M. J. LOBEL[1], L. CUI[2], A. KEIL[3], M. DING[1];
[1]J. Crayton Family Dept. of Biomed. Engin., [2]Biomed. engineering, [3]Dept. of Psychology, Univ. of Florida, Gainesville, FL

Abstract: The Rescorla-Wagner model offers a predictive error-based framework for understanding aversive learning. Although RW-type learning dynamics are well-validated behaviorally, the underlying neural pathways remain poorly understood. We recorded fMRI data from participants (n=18) performing a classical differential fear conditioning task. There were three trial blocks: habituation, acquisition, and extinction. During the habituation block, two Gabor patches (45° and 135°) were presented in random order; no response was required from the subject. During the acquisition block, one Gabor patch, denoted as CS+, was occasionally paired with an aversive human scream (US; 25% reinforcement rate), whereas the other Gabor patch (CS-) was never paired with the US. The extinction block followed the acquisition block where CS+ and CS- were presented without US pairing. Applying univariate GLM contrasts and multivariate SVM decoding of single-trial betas in acquisition, the following results were found. First, the US activated a distributed brain network consisting of auditory cortex, insula,

amygdala, hippocampus, and thalamus. Second, fitting the Rescorla-Wagner model onto single-trial beta values revealed a similar set of brain areas, whose trial-by-trial activation tracked the RW-type learning dynamics. Third, with continued learning, the number of brain areas where CS+ and CS- were decodable became progressively fewer, which at the end of acquisition consisted largely of the same set of areas activated by US. These results suggest that (1) aversive learning at the neural level followed the RW-type of error-driven dynamics and (2) the neural pathways implementing these dynamics were restricted to those that were US-responsive.

Disclosures: M.J. Lobel: None. **L. Cui:** None. **A. Keil:** None. **M. Ding:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.01/II4

Topic: I.09. Spatial Navigation

Support: For grant support see NeuroBatLab website

Title: Mapping the Mammalian Compass System from 3D Head-Direction Space to Natural Behavior

Authors: *Y. FENG[1,3], K. KASUBA[1,3], M. M. YARTSEV[1,2,3,4];
[1]Bioengineering, [2]Neurosci., Univ. of California, Berkeley, Berkeley, CA; [3]Helen Wills Neurosci. Institute, UC Berkeley, Berkeley, CA; [4]Howard Hughes Med. Institute, Univ. of California, Berkeley, Berkeley, CA

Abstract: The mammalian head-direction system is thought to provide an internal compass for navigation, allowing animals to estimate their orientation within the environment. Recent work across species has expanded this framework beyond azimuthal heading, revealing that head-direction circuits can represent three-dimensional orientation and may be organized through structured attractor-like population dynamics. Yet a central question remains unresolved: how neural populations represent the full geometry of 3D head direction, and how this organization relates to the natural structure of self-generated movement. Bats provide a powerful model system for addressing this broader question because their ethological repertoire samples 3D orientation space through flight, landing, and rapid aerial maneuvers in which head direction can vary across azimuth, pitch, and roll. Here, we combined 3D head-direction tracking with large-scale Neuropixels recordings from the dorsal presubiculum and retrosplenial cortex of Egyptian fruit bats across behavioral contexts ranging from controlled rotations to natural and unconstrained aerial behavior. Controlled rotations enabled us to systematically sample the full 3D head-direction space, while spontaneous behavior allowed us to ask how these neural dynamics connect to ethologically relevant, self-generated movement. We found that neurons in the head-direction circuit exhibited tuning to 3D head-direction variables and the direction of rotational movement, while ensemble activity revealed structured and recurrent dynamics that

reflected the evolving geometry of head motion. Information about 3D head direction and rotational movement was embedded in population dynamics across both controlled and naturalistic behavioral contexts, linking ensemble neural activity to complex 3D movement. Together, these results reveal a novel regime of ensemble dynamics through which the mammalian compass system may represent three-dimensional head direction during ethologically relevant behavior in a three-dimensional world.

Disclosures: Y. Feng: None. **K. Kasuba:** None. **M.M. Yartsev:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.02/II5

Topic: I.09. Spatial Navigation

Support: For grant support please see NeuroBatLab website

Title: Motor and Spatial Systems Interaction During Spatial Navigation in Freely Flying Bats

Authors: *X. CHEN[1,2], B. STYR[1,2], M. M. YARTSEV[6,3,4,5,1];
[2]Helen Wills Neurosci. Inst., [3]Biophysics Grad. Group, [4]Howard Hughes Med. Inst., [5]Bioengineering, [1]Univ. of California, Berkeley, Berkeley, CA; [6]Neurosci., UC Berkeley, Berkeley, CA

Abstract: Navigation is one of the most complex and essential behavioral functions across species, requiring precise coordination across sensory, motor, and cognitive domains. In particular, navigation requires movement whereby navigational decisions are both informed by, and must be transformed into, motor actions. To investigate the interaction between motor actions and spatial representations, we performed large-scale (Neuropixels) neural recordings from three brain regions simultaneously in freely flying Egyptian fruit bats: (i) motor cortex, (ii) dorsal hippocampus (HPC) and (iii) medial entorhinal cortex (MEC). In doing so we first discovered a robust oscillatory pattern in the bat motor cortex occurring at the theta frequency band, which emerged during flight and was strongly phase-locked to the wingbeat cycle. This oscillatory activity was not present in the simultaneously recorded HPC or MEC, consistent with previous reports in crawling (Yartsev et al., Nature, 2011) and flying (Forli et al., Nature, 2025) Egyptian fruit bats. Furthermore, many neurons in the motor cortex exhibited strong phase-locking to the theta rhythm, accompanied by increased theta band phase coherence within the motor cortex during flight. The observed motor oscillatory pattern was modulated by behavioral demands such as during flights in the dark, when the bat explored novel routes and during echolocation, a marker for attention in bats. When examining the relationship in neural dynamics between motor cortex and HPC/MEC we observed behaviorally-driven synchronization patterns emerging between the motor and hippocampal systems including (i) theta coherence (ii) and directional information flow, as well as temporal modulation of neuronal firing in both the

hippocampus and MEC by the motor rhythm. Together, these findings reveal a dynamic, cross-regional theta-driven routing system that could support both behavioral and computational needs during navigation. These findings can also provide a potentially unifying mechanism applicable across species, including those that exhibit hippocampal theta (e.g., rodents) and those that do not (e.g., bats, monkeys and humans).

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Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

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Program #/Poster #: PSTR112.03/II6

Topic: I.09. Spatial Navigation

Support: NINDS F31NS143343
Howard Hughes Medical Institute

Title: A Two-Dimensional Grid-Cell Code for Three-Dimensional Navigation in Freely Flying Bats

Authors: *K. K. QI[1], M. M. YARTSEV[1,2,3,4,5];
[1]Biophysics, [2]Bioengineering, [3]Neurosci., [4]Helen Wills Neurosci. Inst., [5]Howard Hughes Med. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: Animals have evolved to navigate environments with diverse geometries and dimensionalities, yet how neural circuits for spatial navigation support behavior across such varied demands remains unresolved. In two-dimensional environments, grid cells in the medial entorhinal cortex provide a periodic signal for self-location that is thought to arise from underlying toroidal attractor dynamics at the ensemble level. However, during movement in three-dimensional environments, studies have reported a loss of global grid-cell periodicity. Furthermore, it remains unknown whether, at the ensemble level, a toroidal attractor is preserved across species and, if so, how such a two-dimensional code could support navigation in three-dimensional space. Here we performed large-scale, wireless neural recordings from the medial entorhinal cortex of freely flying bats engaged in spontaneous aerial foraging. We find that grid cells exhibit robust periodic firing during structured flight trajectories, and that co-modular grid-cell ensembles show topological signatures consistent with a two-dimensional toroidal manifold. Behavioral analyses of bats navigating in the wild and in the laboratory revealed that individual flight paths are organized along two-dimensional planes of motion, providing a natural substrate for a two-dimensional code. Accordingly, toroidal phase along flights was consistent with plane-wave patterns on the plane of motion, and single-cell firing was well described by a hexagonal lattice on the same plane. Together, these findings reveal a parsimonious solution whereby a two-dimensional neural code aligns with behaviorally relevant subspaces to support navigation in a three-dimensional world.

Disclosures: K.K. Qi: None. **M.M. Yartsev:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.04/II7

Topic: I.09. Spatial Navigation

Support: HHMI
NIH Grant NS118422

Title: A Neuro-AI framework for uncovering hippocampal computations during natural behavior in flying bats

Authors: *A. S. LOWET[1], Y. QIU[2], A. FORLI[3], K. KASUBA[1], Y. LIN[2], A. S. TOLIAS[2], M. M. YARTSEV[1];
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Stanford Univ., Stanford, CA; [3]Neurosci. and Brain Technologies, Inst. Italiano di Tecnologia, Quiliano, Italy

Abstract: Transformers and other artificial neural networks (ANNs) have shown promise in relating neuronal spike trains to behavior, outperforming classical approaches such as generalized linear models (GLMs) and scaling more favorably with increasing data. However, ANNs are less inherently interpretable than GLMs and similar methods, which poses a challenge when moving from explaining variance in neural dynamics to developing a deeper understanding of the underlying neural code. Here, we sought to address this gap through a Neuro-AI approach by training Transformers on neural and behavioral data collected from freely-flying Egyptian fruit bats navigating spontaneously in both an indoor flight room and an outdoor field site.
The network consists of a Transformer core to map each flight trajectory into a shared latent space and session-specific readout layers consisting of a linear transformation and a non-linear activation function to transfer to neural responses. The trained model significantly outperformed classical methods, enabling precise prediction of flight-trajectory-dependent firing fields. Additionally, while preserving physical spatial and kinematic variables, the learned latent space emphasizes flight route identity (e.g., origin and destination) as well as behavioral function (e.g., reward and perch), yielding behaviorally grounded invariant representations within each environment that were robustly conserved across animals.
Readout weights, meanwhile, showed meaningful biological structure, differing by hippocampal subregion and surfacing correlations in both spatial and non-spatial activity. This included not only the flight periods on which they were trained (rate maps) but also correlations during non-flight and sleep epochs which were never seen by the model during training. Flipping the direction of the model to decode trajectories from neural input exceeded standard baselines and matched the performance of an optimal, model-based, correlation-aware decoder, demonstrating the utility of integrating across the entire trajectory.
Overall, our findings support a view of the hippocampus not as a passive map of space *per se*,

but as a system that organizes space through the animal's behavior, goals, and actions within it (Whittington et al., 2020; Raju et al., 2024; Zutshi et al., 2025). More broadly, this work establishes a practical and scalable Neuro-AI framework for moving beyond prediction toward discovery: using interpretable, behaviorally grounded models to uncover the computational structure that gives rise to neural activity across the hippocampal formation during rich, natural behavior.

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Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.05/II8

Topic: I.09. Spatial Navigation

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AS Grant AS-CDA-113-L02
National Center for Biomodels (Taiwan)

Title: Explicit Learning Rules Explain Multiscale Representational Dynamics in the Hippocampus

Authors: *C.-L. HSU[1,2,3], H.-Y. WANG[1], H.-T. LIN[4], C.-T. CHEN[8], H.-P. HUANG[9], Y.-C. HUANG[1,5], C. YU[1,6], T.-H. LIU[1,7];
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Abstract: The gradient for deep learning algorithms can be decomposed to, or approximated by, learning rules made of "Three Factors": presynaptic, postsynaptic, and feedback. How realistic is it under real brain dynamics? In the hippocampus, a prominent model for neural learning system, classic models of Hebbian Spike-Timing-Dependent Plasticity (STDP) plus neuromodulation have produced a complex, sometimes difficult-to-interpret rule space.
We demonstrate that hippocampal plasticity conforms to Three-Factor Learning in a simple and elegant way, especially as the non-Hebbian dendritic mechanism of Behavioral Time-Scale Synaptic Plasticity (BTSP) is taken into account. Formally, a unifying theory suggests that dendritic plateau potentials stand at a pivotal position to integrating many factors: translating neuromodulator nonlinear gating unto the biophysics that reads out circuit dynamics and

feedback, consequently controlling bidirectional CA1 synaptic weight update in a finely tuned manner. Finally, our weeks-long Neuropixels recording spanning the primary sensory cortex, entorhinal cortex and all hippocampal subregions from behaving mice exhibited a power of the different rules for explaining cross-areal learning dynamics. Therefore, our work supports a strategy in which construction of explicit learning rules reveals principles of multiscale neural representations regarding synapses, single neurons, and circuits.

Disclosures: C. Hsu: None. **H. Wang:** None. **H. Lin:** None. **C. Chen:** None. **H. Huang:** None. **Y. Huang:** None. **C. Yu:** None. **T. Liu:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.06/II9

Topic: I.09. Spatial Navigation

Support: ERC 101125658

Title: Egocentric Navigation Induces Square Grids: A Computational Account of Distortions in Grid Cells through Reference Frames

Authors: *A. GHOSH[1], A. EPERON[1], F. SIGISMONDI[1], W. REDMAN[2], R. BOTTINI[1]; [1]CIMeC, Univ. of Trento, Trento, Italy; [2]Electrical and Computer Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Grid cells provide an allocentric representation of space, exhibiting regular hexagonal patterns of activity that tessellates the environment. However, deformations in this grid pattern, observed across different environments and tasks, pose a challenge to this theory. In humans, under certain conditions, grid-like signals in the medial entorhinal cortex exhibit a square 90° pattern instead of the typical hexagonal one. We propose that this deformation results from the adoption of an egocentric frame of reference (FoR) during navigation. We test this hypothesis using Recurrent Neural Networks trained to perform path integration. We find that changing the FoR, while maintaining the same architecture and hyperparameters, is sufficient to drive the emergence of distinct representations. Networks trained in an *egocentric FoR (EgoNet) developed a larger number of square units*, whereas networks trained in an allocentric FoR (AlloNet) expressed more hexagonal units. Preliminary results from rodent data (comparing light vs. dark conditions) align with our model findings - darkness shifts grid structure from hexagonal to square. Lesioning the top hexagonal units in EgoNet had negligible effects on path integration, whereas it significantly impaired AlloNet. Conversely, lesioning the top square units caused a drastic performance drop for EgoNet. Only EgoNet exhibited *egocentric center tracking units* and a *non-uniform distribution of head direction units*, with preferred angles clustered around 90° and 270°. Our study provides compelling evidence of how different navigational frames of

reference induce deformed grids, offering testable predictions and a new perspective on the grid cell system through the lens of reference frames.

Disclosures: A. Ghosh: None. **A. Eperon:** None. **F. Sigismondi:** None. **W. Redman:** None. **R. Bottini:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.07/II10

Topic: I.09. Spatial Navigation

Support: SFB-1436/2 project ID 425899996
Advanced ERC grant project ID 101142587

Title: Visual landmarks drive rapid reorientation of grid cell population activity during goal directed navigation

Authors: *F. JOSE KAVARAYIL, B. THROM, K. ALLEN, H. MONYER;
Dept. of Clin. Neurobio., Med. Fac. of Heidelberg University, and German Cancer Res. Ctr. (DKFZ), Heidelberg, Germany

Abstract: Grid cells in the medial entorhinal cortex (MEC) provide a fundamental neural representation of space and are thought to contribute to spatial navigation by generating an internal metric for self-location. Previous studies have shown that visual landmarks stabilize grid cell firing patterns and that manipulations such as visual cue rotations induce coherent reorientation of grid representations. However, these effects have primarily been examined using spatial firing maps averaged over extended recording periods. Thus, little is known about how grid cell representations adapt during brief, behaviorally relevant visual events occurring on the timescale of seconds. To address this, we developed a fully automated, visually guided navigation task in which four display screens surrounding a circular arena generated distal visual landmarks. Mice learned to associate specific visual configurations with reward locations; task execution, reward delivery, and data acquisition were performed without human intervention. Visual cue configurations were systematically rotated between trial blocks, while neuronal activity in the MEC was recorded using high-density silicon probes. To investigate rapid changes in grid cell activity, we employed a long short-term memory (LSTM)-based decoding approach to reconstruct grid cell spatial representations. Grid cells were identified during random-foraging control sessions, and population activity was projected onto toroidal coordinates, thereby avoiding prediction ambiguity inherent to the periodic nature of grid cell firing. Rotations of visual cue configurations induced rotations in reconstructed grid orientation detectable at the population level during ongoing task performance. These effects occurred during behaviorally relevant epochs and were resolved at a substantially finer temporal scale than conventional occupancy-normalized firing rate map analyses. These findings demonstrate that grid cell

population activity rapidly reorients in response to visual landmark changes during goal-directed navigation, highlighting the utility of toroidal reconstruction for investigating dynamic reference-frame transformations within the entorhinal spatial navigation system.

Disclosures: F. Jose Kavarayil: None. **B. Throm:** None. **K. Allen:** None. **H. Monyer:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.08/II11

Topic: I.09. Spatial Navigation

Title: Circuit Mechanisms of Reference Frame Selection During Spatial Reorientation

Authors: P. M. OGALLAR[1], M. E. NORMANDIN[1], C. M. GAGLIARDI[2], ***I. A. MUZZIO**[1]; [1]Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA; [2]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Spatial reorientation—the ability to recover one's bearings after becoming disoriented—requires the flexible selection of spatial reference frames based on environmental geometry and learned landmark information. While geometric cues provide a stable directional reference following disorientation, landmarks are inherently less reliable because they can change position or aspect across experiences; however, they offer greater spatial precision once they acquire directional significance. The neural mechanisms that arbitrate between these cues remain poorly understood. We hypothesized that the retrosplenial cortex (RSC) serves as a critical hub for reference frame selection by integrating visual, directional, and mnemonic signals across its granular (gRSC) and dysgranular (dRSC) subdivisions. Furthermore, we proposed that this computation is regulated by two complementary hippocampal inputs: a long-range GABAergic CA1→gRSC projection that gates geometry-based reference frame selection and a glutamatergic dorsal subiculum (dSub)→gRSC projection that promotes landmark-based reference frame selection. To test these hypotheses, we trained mice in a spatial reorientation task and examined RSC function using pathway-specific optogenetics, chemogenetics, and longitudinal calcium imaging. We first characterized the functional contributions of gRSC and dRSC and tracked the evolution of spatial representations as animals transitioned from an initial reliance on geometry to the use of learned landmark information. We found that dRSC was critical for early geometry-based reorientation and displayed geometry-anchored representations before animals learned the task. In contrast, gRSC contributed to both geometric and landmark-guided navigation, exhibiting a gradual shift from geometry-dominated to landmark-based representations as learning progressed. Optogenetic activation of CA1→gRSC GABAergic projections disrupted geometry-based reorientation while producing only modest effects on landmark-guided behavior. Conversely, optogenetic inhibition of dSub→gRSC glutamatergic projections prevented the use of learned landmark information and prolonged reliance on geometric strategies. Together, these findings identify complementary hippocampal-retrosplenial

circuits that regulate the selection of competing spatial reference frames during navigation. More broadly, they reveal a circuit mechanism by which the brain dynamically weights stable and learned sources of information to support flexible behavior, providing insight into a form of cognitive control that underlies cue competition.

Disclosures: P.M. Ogallar: None. **M.E. Normandin:** None. **C.M. Gagliardi:** None. **I.A. Muzzio:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.09/II12

Topic: I.09. Spatial Navigation

Support: Simons foundation SCGB

Title: Latent State Models Reveal Cyclic Behavioral Policies and Hippocampal Goal-Distance Integration During Labyrinth Navigation

Authors: *Z. JING[1], J. WU[2], M. MEISTER[2];
[1]BBE, [2]Caltech, Pasadena, CA

Abstract: Naturalistic maze navigation requires organizing behavior and neural computation across multiple timescales. In a six-level binary-tree labyrinth, mice learn to reach a reward port after about ten reward experiences, often exhibiting a sudden step increase in performance termed "sudden insight" (Rosenberg et al., 2021). We ask how this learning is reflected at both the behavioral and neural levels using complementary latent state models. To characterize behavior, we applied an input-output Hidden Markov Model (IOHMM) to parse mouse trajectories into episodes reflecting distinct navigation policies. A four-state model generalized across animals and identified interpretable strategies—water-seeking, homing, and two forms of exploration—arranged in a cyclic transition structure. A hierarchical extension revealed an abrupt shift from naive to expert policies coinciding with the sudden performance increase. To examine the neural substrate of these policies, we fit an adapted recurrent switching linear dynamical system (rSLDS) to simultaneously recorded hippocampal CA1 population activity (~1000 neurons per animal), with location and head direction as inputs. Three discrete latent states emerged—exploration, reward-seeking, and reward-consuming—with continuous latent variables capturing variance beyond place and head-direction tuning. Within the reward-seeking state, a line-attractor-like dimension tracked the animal's distance toward the water port, resetting through reward-consuming relaxation dynamics at each reward episode. An analogous sequence occurred at a symmetrically located "illusory port", but the continuous variable rewound prematurely before reaching the line attractor endpoint. Critically, the frequency of these illusory reward-state episodes showed a step decrease before the sudden insight moment, suggesting that disambiguating this illusory reward port from the true reward port underlies the sudden

performance improvement. Together, the behavioral and the neural latent state models reveal a shared discrete state structure underlying maze navigation: mice periodically sequence a small repertoire of behavioral policies while hippocampal CA1 encodes distance-to-goal through a state-gated line attractor, with sudden insight emerging from the disambiguation of reward-port-symmetric locations.

Disclosures: Z. Jing: None. **J. Wu:** None. **M. Meister:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.10/II13

Topic: I.09. Spatial Navigation

Support: NIH Grant 1P50MH136296

Title: A New Paradigm to Study Learning to Navigate to Goals Without Immediate Rewards

Authors: *S. XIANG, Y. ZHANG, Y. SAGIV, S. N. OLINE, N. D. DAW, I. B. WITTEN; Princeton Univ., Princeton, NJ

Abstract: Latent learning is the phenomenon of acquiring knowledge about spatial environments in the absence of explicit and immediate reinforcement. Animals such as rodents can later use this information to guide flexible navigation decisions. Classical latent learning paradigms, however, are limited by “one-shot” experimental designs that restrict repeated within-subject assessment. Here, we developed a repeatable latent learning task using a reconfigurable maze with movable doors that generate novel spatial layouts. During the Pre-exposure phase, mice freely explored the maze in the absence of reward. During a subsequent Test phase, reward became available as indicated by a visual cue near the reward location. To assess latent learning, mice were tested in either “match” sessions, in which maze structure remained unchanged between Pre-exposure and Test, or “mismatch” sessions, in which maze configuration was altered immediately after Pre-exposure. Five mice were tested in the behavioral task. We quantified first-trial excess state sequence length, defined as the difference between actual and optimal path lengths. All animals successfully learned the cue-reward association, reaching correct trial performance well above chance within the first few sessions. In the first Test trial of the match sessions, mice were readily able to take the optimal path. This is contrasted by the mismatch sessions, in which mice exhibited significantly greater first-trial excess state sequence lengths. This suggests that animals relied on spatial knowledge acquired during unrewarded pre-exposure to guide subsequent navigation behavior. Together, these findings establish a repeatable behavioral task for studying latent learning and flexible spatial navigation. Ongoing experiments include testing whether dorsomedial striatum activity is required for performing multi-goal sequential navigation in the maze using reversible muscimol-mediated inactivation.

Disclosures: S. Xiang: None. **Y. Zhang:** None. **Y. Sagiv:** None. **S.N. Oline:** None. **N.D. Daw:** None. **I.B. Witten:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.11/Web Only

Topic: I.04. Executive Functions

Support: PROSNII-2026

Title: Behavioral flexibility in CD1 mice: comparison between females and males in the Dashiell maze

Authors: *L. MARQUEZ ROJAS[1], J. BURITICÁ[1], F. CABRERA[2], I. ZEPEDA[2], T. V. CAMPOS ORDONEZ[3];
[1]Ctr. de Estudios e Investigaciones en Comportamiento, Univ. de Guadalajara, Guadalajara, Mexico; [2]Ctr. Universitario de la Ciénega. Ctr. de Investigaciones en Conducta y Cognición Comparada., Univ. de Guadalajara, Ocotlán, Mexico; [3]Ctr. Universitario de Ciencias Biológicas y Agropecuarias, Univ. of Guadalajara, Zapopan, Mexico

Abstract: The Dashiell maze is an experimental apparatus composed of multiple corridors and bifurcations, traditionally used to evaluate exploration in rats and humans. In this study, we adapted the paradigm for adult male and female CD1 mice, incorporating additional phases to analyze behavioral flexibility, defined as the ability of organisms to modify their responses in response to changes in environmental contingencies. The procedure was carried out in four phases. The first phase consisted of six days with two trials per day, applying the conventional Dashiell maze with a goal containing five 14 mg diet pellets as reinforcement. The second phase, Flexibility 1, lasted three days with two trials per day, incorporating two new goals and blocking the original one. The third phase, Flexibility 2, was conducted over three days, blocking one of the additional goals according to each subject's prior preference to redirect the animal to the alternative. Finally, the fourth phase restored the conventional maze for three days. Nine CD1 mice participated in the study, five females and four males, aged 92 PND. They were maintained at 85% of their body weight through food deprivation and reinforced with pellets upon reaching the goal. The time taken to complete each trial was recorded. Results showed no significant sex differences in most phases. However, in the first flexibility phase, males exhibited significantly longer completion times (137.8 ±70.24 s) compared to females (35.4 ± 25.42 s). This finding suggests lower efficiency or greater difficulty in abandoning the previously learned route when faced with an abrupt change in the available goals. In contrast, females demonstrated faster adaptation. In conclusion, these findings indicate sex differences in behavioral flexibility under conditions of change in the Dashiell maze.

Disclosures: L. Marquez Rojas: None. **J. Buriticá:** None. **F. Cabrera:** None. **I. Zepeda:** None. **T.V. Campos Ordonez:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.12/II14

Topic: I.09. Spatial Navigation

Support: CIHR Project Grants 180330
CIHR Project Grants 190289
NSERC Discovery Grants RGPIN-2025-06801
FRQS Doctoral Research Scholarship 332942

Title: Inhibitory coordination of thalamic head direction cells

Authors: *H. DENNY[1], M. Q. LIU[1], A. PEYRACHE[2];
[2]Montreal Neurolog. Inst., [1]McGill Univ., Montreal, QC, Canada

Abstract: Neurons in the head direction (HD) system fire for specific angles of the head in the horizontal plane, acting as the animal's compass. Remarkably, in the anterodorsal nucleus (ADN) of the thalamus this signal is very stable; correlations between ADN-HD neurons are maintained during sleep despite the deprivation of sensory information. Indeed, a "virtual" HD not only persists during sleep but rapidly rotates around the compass, suggesting that the HD signal is to some extent internally generated. These properties are consistent with attractor-like dynamics, and computational models suggest such a network requires two features to function: recurrent connections, and global inhibition. We hypothesized that the Thalamic Reticular Nucleus (TRN), a nucleus of inhibitory neurons reciprocally connected to the ADN, is the instrumental in supporting attractor-like dynamics for ADN-HD neurons. In this work, we used 8-shank silicon probes targeting the anterior thalamus to simultaneously record multi-unit activity from the ADN and TRN. Animals were allowed to sleep in their home cage for 2 hours, before being placed in an open field arena to explore for 15 minutes. Based on functional coupling and HD tuning parameters, we found a restricted sector of the TRN connects recurrently to the ADN. To causally test whether these functional connections support ADN attractor dynamics, we selectively inhibited ADN-projecting TRN terminals by expressing ArchT in the TRN of VGAT-Cre mice, then implanted an optical fiber and silicon probe to the ADN. Optogenetic silencing of TRN terminals in the ADN resulted in transient collapse of pairwise correlations between ADN-HD neurons, suggesting a disruption of attractor-like dynamics. These findings shed light on how the TRN contributes to signal generation in the thalamocortical networks.

Disclosures: H. Denny: None. **M.Q. Liu:** None. **A. Peyrache:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.13/II15

Topic: I.09. Spatial Navigation

Support: CIHR Project Grant 180330
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NSERC Discovery Accelerator Supplement: RGPAS-2020-00031
CIFAR (Canada AI Chair; Learning in Machine and Brains Fellowship)

Title: Complementary roles of spatial tuning and population geometry in place- vs. memory-guided navigation

Authors: *A. EFREMOV[1], D. LEVENSTEIN[3], B. A. RICHARDS[2], A. PEYRACHE[1];
[1]Montreal Neurolog. Inst., [2]Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada;
[3]Neurosci., Yale Univ., New Haven, CT

Abstract: Mammals' ability to navigate depends on the hippocampus, which constructs a cognitive map of the environment. While navigation can be driven without hippocampal involvement, its contributions are needed for rapid adaptation to new tasks and conditions. The reasons for this adaptability, whether through place cell coding of spatial features or population-level hippocampal processing, remain an open question.
In this work, we explored a hippocampal-striatal model solving navigational tasks. We modeled the hippocampus as a recurrent neural network trained to predict sequences of observations, which developed spatially tuned cells and captured environmental geometry on a population level. We trained reinforcement learning agents to use hippocampal states or egocentric visual input to solve a navigational task with visual ambiguities. We found that access to hippocampal activity enabled agents to learn the task successfully, unlike access to egocentric visual input only. This capacity was directly related to spatial information contained in individual RNN units, rather than the network's population-level representation.
We next wondered whether using hippocampal representations to estimate distance to a goal improves the performance and developed an algorithm that uses cognitive maps to identify an agent's movement towards or away from a remembered representation of the goal and provides it with corresponding reinforcement. We found that agents using this algorithm were more efficient than those with full observability of the environment.
Finally, we investigated whether the cognitive maps learned by our model enable agents to navigate to any arbitrary location. We trained agents in a goal-conditioned task, where in each episode, agents had to navigate to a new random goal while having access to the hippocampal representation of the goal location. The performance in this task was highly dependent on the model's ability to preserve environmental geometry. Specifically, a high correlation between spatial and corresponding neural distances was predictive of faster learning and higher accuracy in the task. In contrast, agents whose hippocampal representations didn't preserve distances were

unable to learn the task, even though individual hippocampal neurons provided high spatial information.
Our results indicate that combinations of individual place cells can provide enough spatial information to serve as stimuli in stimulus-response behavior. However, hippocampal population-level representations and dynamics can provide an intrinsic learning signal to facilitate performance and allow for generalization in navigation.

Disclosures: A. Efremov: None. **D. Levenstein:** None. **B.A. Richards:** None. **A. Peyrache:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.14/II16

Topic: I.09. Spatial Navigation

Support: CIHR Project Grant 180330
CIHR Project Grant 190289
NSERC Discovery Grant RGPIN-2025-06801
CIHR Canada Graduate Scholarship Doctoral

Title: Thalamic head direction cells exhibit structured visual receptive fields

Authors: *M. Q. LIU[1,3], S. TRENHOLM[2,3], A. PEYRACHE[2,3];
[1]Integrated Program in Neurosci., [2]McGill Univ., Montreal, QC, Canada; [3]Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Background: Orienting ourselves is crucial for navigating our environment, and visual cues are particularly informative in enabling our brain's spatial navigation systems to stably anchor our own position relative to the external world. In the head direction (HD) system, salient wall-mounted visual landmarks control the preferred firing directions of HD cells, and placing animals in the dark results in unstable HD cell tuning. Moreover, recent work has shown that visual inputs directly modulate HD cell firing—visually responsive HD cells in the postsubiculum modulate their firing in response to a visual cue directly facing the animal, and the valence of this response (i.e., excitation or inhibition) varies with angular tuning. However, the precise nature of the interaction between HD and visual input in shaping HD coding at the single cell and population levels remains unknown. Here, we investigate whether HD cells have spatially localized visual receptive fields, whether their receptive fields contain excitatory and inhibitory regions, and if, at the population level, visual receptive field responses vary as a function of HD tuning. Methods: Using high density silicon probes in freely moving mice, we recorded from HD cells in the anterodorsal nucleus (ADn) of the thalamus, the input to the postsubiculum. We then head-fixed the mice and presented visual stimuli from four surrounding monitors. The head-fixation platform was dynamically rotated throughout the experiment to

capture how visual responses changed with the animal's HD. Results and Conclusions: We found that HD cells have visual receptive fields with spatially localized excitatory and inhibitory regions. The position of the excitatory region varies along the azimuth, with different HD cells exhibiting different receptive field configurations. Whether the preferred firing direction of HD cells relates to the spatial configuration of their visual receptive fields, and how exactly visual receptive fields change as a function of HD are questions that we are continuing to explore.

Disclosures: M.Q. Liu: None. **S. Trenholm:** None. **A. Peyrache:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.15/II17

Topic: I.09. Spatial Navigation

Support: Simons Foundation SFI-AN-AR-Rat Models-00014377-02

Title: Long-Term Stability and Context-Dependent Reorganization of Spatial Coding in the Postsubiculum and Retrosplenial Cortex of Wild-Type and Fmr1-KO Rats

Authors: *N. CHAHINE[1], Y. WANG[2], A. PEYRACHE[3];
[1]Integrated Program in Neurosci., McGill Univ., Montreal, QC, Canada; [2]McGill Univ., Montréal, QC, Canada; [3]Montreal Neurolog. Inst., McGill Univ., Montreal, QC, Canada

Abstract: Spatial navigation relies on the integration of allocentric and egocentric reference frames. The postsubiculum (PoSub), a key node of the head-direction system, and the retrosplenial cortex (RSC), which contributes to contextual memory and spatial cognition, are critical components of the navigation network. However, the long-term stability of their spatial representations remains poorly understood. Here, we investigated the longitudinal dynamics of spatial tuning in wild-type (WT) and Fmr1-KO rats, a well-established model of Fragile X syndrome. Using in vivo calcium imaging with miniaturized microscopes, we tracked the same neuronal ensembles in the PoSub and RSC over two months. To dissociate temporal drift from context-dependent changes in spatial coding, rats foraged in three distinct environments that differed in exploration frequency and duration. In WT animals, allocentric and egocentric tuning remained remarkably stable within a given environment, regardless of how often it was visited. However, representations changed reliably across environments. Notably, PoSub ensembles preserved their internal organization while exhibiting coherent shifts in directional tuning, whereas RSC representations displayed strong context specificity. We are currently evaluating Fmr1-KO animals to determine how loss of FMRP affects the balance between long-term stability and context-dependent reorganization. Together, these findings suggest that PoSub and RSC maintain durable yet flexible spatial representations over extended timescales, providing a framework for understanding spatial coding in both healthy and Fragile X circuits.

Disclosures: N. Chahine: None. **Y. Wang:** None. **A. Peyrache:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.16/II18

Topic: I.09. Spatial Navigation

Support: Canadian Institutes of Health Research Project Grants 190289 and 180330
National Sciences and Engineering Research Council Discovery Grant RGPIN-2025-06801

Title: A neural phase transition marks the onset of sleep.

Authors: *A. PEYRACHE[1], Y. WANG[2];
[1]McGill Univ., Montreal, QC, Canada; [2]McGill, Montréal, QC, Canada

Abstract: As the body transitions from wakefulness to sleep, the electroencephalogram undergoes major changes. Yet precise markers of the sleep onset process remain elusive. Here, we investigated the dynamics of thalamic head-direction (HD) cells, which maintain coherent population-level tuning across all brain states, yet drift randomly relative to the animal's actual heading direction during sleep. We hypothesized that the moment when the HD cell population decouples from the animal's actual heading direction constitutes a precise marker of sleep onset. We show that this decoupling coincides with a decrease in electromyogram (EMG) activity, and that the transition from coupled to uncoupled population dynamics is an abrupt, non-linear function of EMG amplitude, consistent with a phase transition in the physical sense. Together, these findings provide an operational definition of sleep onset in mammals, with direct implications for characterizing the physiological and cognitive changes unfolding at the wake-sleep boundary.

Disclosures: A. Peyrache: None. **Y. Wang:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.17/II19

Topic: I.09. Spatial Navigation

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Howard Hughes Medical Institute
Japan Society for the Promotion of Science
Klingenstein Fellowship

Title: Superior colliculus silencing differentially affects head direction cells across REM and non-REM sleep

Authors: *T. GERELMAA[1], M. SCANZIANI[2,3], Y. SENZAI[1,3,2];
[1]Northwestern Univ., Chicago, IL; [2]Dept. of Physiol., Univ. of California San Francisco, San Francisco, CA; [3]Howard Hughes Med. Inst., San Francisco, CA

Abstract: Animal sleep consists of two distinct phases: rapid eye movement (REM) sleep and non-REM (NREM) sleep. Theoretical and computational studies suggest that offline interactions between sensory-motor and navigation systems during these sleep states may play distinct roles in learning and memory. However, experimental evidence supporting this idea remains limited. We recently showed that, during REM sleep, activity in the deep layers of the mouse superior colliculus (SC), a motor center for head movements, predicts shifts in the internal representation of heading decoded from head direction (HD) cells in the anterodorsal nucleus of the thalamus. Furthermore, silencing the superior colliculus in one hemisphere, a manipulation that in awake animals causes continuous turning (circling), causes circling of the internal heading representation in the same direction during REM sleep, despite the animal's immobility. However, it is not clear whether a similar coordination between the SC motor layer and the HD system exists during NREM sleep. Here, we tested whether unilateral SC silencing with tetrodotoxin also biases the internal heading representation during NREM sleep. To decode the internal representation of heading during NREM sleep, we applied a state-space model (Denovellis et al., 2021) to identify temporally compressed "sweeps" in the HD cells. In contrast to REM sleep, where right SC silencing produced a significant clockwise bias in heading shifts, SC silencing had little effect on the average direction of HD sweeps during NREM sleep. These results demonstrate that the influence of the SC on the thalamic HD system depends strongly on sleep state. The distinct effects of SC silencing across REM and NREM sleep suggest that offline processing in these two sleep states may serve different computational functions.

Disclosures: T. Gerelmaa: None. **M. Scanziani:** None. **Y. Senzai:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.18/II20

Topic: I.09. Spatial Navigation

Support: NIH Grant R00 EY033850
Klingenstein Fellowship

Title: Visual receptive fields of the head direction cells in the anterodorsal nucleus of the thalamus

Authors: *K. CAO, A. ADEWAKUN, E. BELLUCCINI, Y. SENZAI;
Neurosci., Northwestern Univ., Chicago, IL

Abstract: Accurate navigation requires animals to maintain an internal estimate of allocentric heading despite noisy self-motion signals and changing sensory inputs. Head direction (HD) cells provide a neural representation of heading: each cell fires maximally when the animal faces a particular direction, and population activity across HD cells serves as an internal compass for orientation. In rodents, HD cells have been identified throughout a distributed network of cortical and subcortical areas. While self-motion cues such as vestibular signals can update head direction (HD) representations through bottom-up pathways involving the dorsal tegmental nucleus, lateral mammillary nucleus (LMN), and anteriodorsal nucleus of the thalamus (ADN), stable HD representations also require anchoring to visual landmarks. Previous studies suggest that top-down inputs from cortical areas to the LMN and the ADN contribute to visual anchoring of HD representations. However, the circuit mechanisms through which visual landmark information shapes HD representations remain poorly understood. To address this question, we characterized visual receptive fields of ADN HD cells. We found that ADN HD cells preferentially represent the upper visual field rather than the lower visual field. This finding is consistent with the idea that distal visual landmarks, rather than proximal cues, play a dominant role in stabilizing HD representations. Furthermore, the presence of structured visual receptive fields in ADN HD cells suggests that the ADN may not simply relay cortical HD representations already anchored to visual landmarks, but may itself participate in the computation of visual anchoring for the head direction system.

Disclosures: K. Cao: None. **A. Adewakun:** None. **E. Belluccini:** None. **Y. Senzai:** None.

Poster

PSTR112: Place, Direction, and Navigation I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR112.19/II21

Topic: I.09. Spatial Navigation

Support: Howard Hughes Medical Institute
Jane Coffin Childs Memorial Fund

Title: Evidence of an internal model from the superior colliculus to the head direction system

Authors: *A. LEVI, M. R. STINGL, M. SCANZIANI;
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Abstract: The ability of the brain to predict consequences of its own actions is a hallmark of cognition. Such predictions rely on internal models, transformations of motor commands into

expected sensory outcomes, even when the command is not executed. The head direction (HD) system, a population of neurons that reports the animal's heading, is updated by a motor-sensory feedback loop in which motor commands to turn the head lead to shifts in the HD representation. The Superior Colliculus (SC), a midbrain motor command center, generates orienting head turns. While correlations between SC activity and the HD system have been shown, whether SC motor commands causally update the HD system as part of an internal model remains unknown. We performed extracellular recordings from the anterior dorsal nucleus (ADN), an area abundant with HD cells, while tracking the heading of freely-moving mice using a camera system. We trained a Bayesian decoder to estimate head direction from HD cell population activity, allowing us to evaluate the virtual HD - the direction to which the HD system is pointing. Simultaneously, we optogenetically activated motor neurons in the SC. During wake, activation of the SC reliably generated head turns and the virtual HD shifted accordingly. During REM sleep, a state characterized by muscle atonia, SC activation did not produce physical head movements. However, decoding of the HD cells' activity revealed a clear shift in the virtual HD, as if the animal had turned its head. These results provide causal evidence that motor commands issued by the SC update the HD system, independently of sensory feedback, supporting the existence of an internal model linking the SC to the HD system.

Disclosures: A. Levi: None. **M.R. Stingl:** None. **M. Scanziani:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.01/II22

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

Support: NIH Grant GM140841

Title: Amplified MS2 labeling reveals heterogeneous dynamics of RNA granules in the live murine brain ex vivo

Authors: *H. LIM, G. P. COOPER;
Indiana Univ., Bloomington, IN

Abstract: Dynamics of messenger ribonucleic acids (mRNAs) and the complexes with associated proteins (RNPs), also known as RNA granules, provide post-transcriptional control of gene expression. This regulation is crucial for cell-type diversity and activity-dependent plasticity of the mammalian central nervous system (CNS). However, elucidating the physiological significance of RNA granules has been hampered by the lack of technologies for probing them in live brain. Here, we describe a novel method to visualize RNA granules in native CNS tissues of mouse. To amplify the fluorescence signal from single mRNAs incorporating MS2 stem loops, MS2 capsid protein (MCP) was conjugated with 4 tandem superfolder green fluorescent proteins (sfGFPs). Using MCP-4×sfGFP, a substantial population

of RNPs could be probed in specific cells of the CNS, enabling new findings, e.g., remarkable heterogeneity of *Actb* mRNA dynamics across neurons and glial cells. The highly sensitive in vivo RNA imaging could be useful for illuminating the regulation of the dynamics of RNA granules in naive and diseased animal models.

Disclosures: H. Lim: None. **G.P. Cooper:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.02/II23

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

Support: Brain Science and Brain-like Intelligence Technology - National Science and Technology Major Project Grant 2021ZD0204401
Brain Science and Brain-like Intelligence Technology - National Science and Technology Major Project Grant 2021ZD0204503
NSFC Grant 32125020
NSFC Grant 32371072
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NSFC Grant 32300936
Shanghai Committee of Science and Technology Grant 22JC1403101
Strategic Priority Research Program of the Chinese Academy of Sciences Grant XDB1010102
China Postdoctoral Science Foundation Grant 2023M743609
China Postdoctoral Science Foundation Grant BX20240389

Title: Integrating gene expression and subcellular RNA localization with other modalities in thick tissue

Authors: *X. LIU, Y. ZHAO, Z. SHI, L. CONG, L. BAI, L. GU, C. CHEN, K. WANG, S. XU; Ctr. for Excellence in Brain Sci. and Intelligence Technol. (Institute of Neuroscience), Chinese Acad. of Sci., Shanghai, China

Abstract: Spatial transcriptomics has emerged as a powerful tool for mapping gene expression within its naive tissue context. Expansion-based spatial transcriptomics in thick tissue further extends this capability by revealing the three-dimensional subcellular distribution of RNA within intact cells. However, the technical complexity of hydrogel expansion and the difficulty of integrating this ISH platform with other modalities—such as functional imaging and whole-brain projection tracing—mean that obtaining multimodal information from the same neuron remains an unsolved challenge. Here, we developed a dual-color spatial transcriptomics technique for thick tissue, termed 2cEASI-FISH, and seamlessly integrated it with in vivo two-photon calcium imaging and whole-brain projection tracing. This enables the simultaneous acquisition of gene

expression, subcellular RNA localization, functional activity, and projection architecture from the same individual neurons in the mouse primary visual cortex. Functioning like a "one-shot" cinematic sequence, this platform captures the comprehensive multimodal landscape of single neurons. Using this approach, we unexpectedly revealed that a subset of cortical excitatory neurons co-expresses inhibitory markers, with these specific mRNAs sequestered within the nucleus. Together, these results demonstrate that our thick-tissue spatial transcriptomics platform offers exceptional scalability and adaptability, positioning it as a versatile foundation for future explorations of gene expression and cellular organization in complex biological systems.

Disclosures: X. Liu: None. **Y. Zhao:** None. **Z. Shi:** None. **L. cong:** None. **L. Bai:** None. **L. Gu:** None. **C. chen:** None. **K. Wang:** None. **S. Xu:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.03/II24

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

Support: NIH NIDA grant DP1DA056018

Title: Single-chromatin fiber profiling links rDNA enhancer repeat variation to distinct epigenetic and transcriptional states in the mouse hippocampus

Authors: *Y. ZHU, A. HARNETT, S. AKBARIAN;
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Abstract: Background: The mammalian genome contains hundreds of ribosomal DNA (rDNA) copies, with each copy defined by an enhancer repeat (ER), located between the spacer promoter (SP) and the 47S pre-rRNA promoter (47P), and have been shown to enhance RNA Polymerase I transcription. Fiber-seq is a long-read single-molecule sequencing approach that uses methyltransferase Hia5 to label accessible chromatin via m^6A modifications while simultaneously detecting endogenous 5mCpG signals, enabling us to resolve sequence variation and epigenetic features within the same rDNA copy for the first time. **Methods:** Adult C57BL6 mouse ventral hippocampal(vHc) tissue was subjected to single molecule PCR amplification free 12Kb chromatin fiber Fiber-seq and 5Kb rRNA sequencing. **Results:**1. rDNA genotype. We identified eight discrete ER length classes (L1-L8), ranging from 834 bp (L1) to 2,590 bp (L8), each defined by a characteristic unit composition. Except for L3, which comprises two subtypes (L3.1 and L3.2), reads within each class share >90% sequence similarity. The eight classes were grouped into four major types (L1/2, L3, L4/5, L6/7/8), each associated with distinct variant signatures in the 28S rRNA coding region. 2. rDNA epigenetic states. Analysis of 3,878 full-length rDNA reads revealed three epigenetically distinct chromatin states: active (16.3%, high m^6A, low 5mCpG, nucleosome-free), poised (63.1%, low m^6A, low 5mCpG, nucleosome-occupied), and silent (15.6%, low m^6A, high 5mCpG, nucleosome-occupied).The four major ER

types showed distinct epigenetic preferences: L1/2 and L4/5 exhibited significantly higher DNA methylation than L3 and L6/7/8, while L3 and L6/7/8 were enriched in the active states and depleted in the silent states. 3. rRNA expression. Using type-specific 28S variant signatures, individual rRNA transcripts were assigned to their fiber type of origin. L1/2 and L4/5 were underrepresented in the rRNA pool relative to their genomic abundance (L1/2: observed 15.5% vs. expected 20.1%; L4/5: observed 19.4% vs. expected 39.4%), whereas L3 and L6/7/8 were overrepresented (L3: observed 42.4% vs. expected 24.3%; L6/7/8: observed 22.7% vs. expected 16.2%), demonstrating that ER genotype-associated epigenetic states directly determine rRNA transcriptional output. **Conclusion:** rDNA copies in the mouse ventral hippocampus form distinct genotypic and epigenetic subpopulations, with ER structural variation linked to chromatin state and transcriptional activity. This work establishes a single-molecule framework for dissecting rDNA heterogeneity and its role in regulating ribosome biogenesis in the brain.

Disclosures: Y. Zhu: None. **A. Harnett:** None. **S. Akbarian:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.04/II25

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

Support: Simons Foundation Shenoy Undergraduate Research Fellowship in Neuroscience

Title: Parcellation of the midbrain reticular formation using spatial transcriptomics

Authors: *R. H. YIN[1,2], N. A. STEINMETZ[2];
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Abstract: Visual perception and decision-making depend on the dynamic activity across a wide range of brain regions, from the frontal cortex to the hindbrain. The midbrain reticular formation (MRF) is a brainstem structure implicated in brain-wide coordination during visual decisions, receiving input from cortex and basal ganglia and projecting broadly to targets in thalamus, midbrain, and hindbrain. However, the biological structure of the MRF has not been well characterized and it remains largely unknown whether its diverse molecular, biophysical, and functional properties reflect subregional organization. Here we investigate this possibility by considering the spatial organization of neurons identified by their gene expression with spatial transcriptomics (MERFISH, Yao et al. 2023). We applied seed pixel correlation to spatial transcriptomic datasets registered to the Allen Common Coordinate Framework, selecting seed locations across midbrain regions surrounding the MRF. Each seed's local cell type profile was correlated across the MRF volume. Inferior colliculus, anterior pretectal nucleus, and substantia nigra pars reticulata seeds produced spatially non-overlapping correlation patterns, suggesting that independent zones of MRF are closely related in their cell type composition to neighboring structures. Examinations of individual cell types support this; for example, three glutamatergic

cell types determined by Tfap2d, Maf, Six3, and En2 transcription factor marker genes are densely and exclusively clustered in the inferior colliculus and in a dorsal-posterior corner of MRF. Ongoing work incorporates datasets including viral connectivity tracing, single-neuron morphology, spike waveform properties, and 4-shank Neuropixels 2.0 probe recordings. Alignments across modalities will reflect whether molecularly identified subregions can support biologically meaningful parcellation. This comprehensive map of the MRF provides a framework for understanding MRF contributions to brain-wide coordination.

Disclosures: R.H. Yin: None. **N.A. Steinmetz:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.05/II26

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

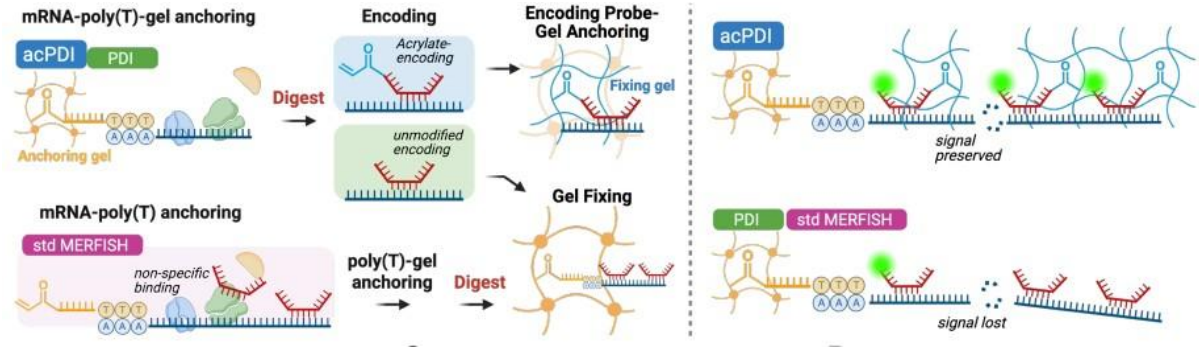
Support: NIH R35GM147420

Title: A-Locked FISH: robust, sensitive, and widefield volumetric spatial transcriptomics

Authors: *Z. STARR[1], Q. FENG[2];
[1]Univ. of Illinois Urbana-Champaign, Hinsdale, IL; [2]Chem., Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Champaign, IL

Abstract: Spatial transcriptomics is rapidly expanding our ability to map gene expression within intact tissues, providing new insight into development, behavior, and disease. However, major challenges remain in maintaining signal stability during imaging-based spatial transcriptomic experiments. In MERFISH, encoding probes are retained through hybridization to target RNA, making signal preservation dependent on RNA integrity and limiting robustness during repeated stripping, prolonged storage, and tissue processing. Existing approaches often require specialized cleavable-probe chemistries or compromise transcript recovery. Here, we developed A-Locked FISH, a MERFISH-compatible strategy in which 5′ acrylate-modified encoding probes are hybridized after tissue digestion (acPDI) and covalently anchored within the hydrogel matrix, decoupling signal retention from RNA integrity (Fig. 1). In honey bee brain tissue, acPDI reduced signal loss during stringent formamide stripping from 21.5% to 8.3%, preserving probe signals across repeated imaging cycles without specialized cleavable-probe chemistry. AcPDI also nearly doubled transcript detection relative to standard expansion MERFISH and maintained detection efficiency after 60 days of storage at 4°C, demonstrating improved transcript accessibility and long-term sample stability. Furthermore, RNA-independent signal retention enabled extensive enzymatic removal of untargeted RNA to suppress background fluorescence. This increased the spot-level signal-to-noise ratio from 1.64 to 3.55 and enabled rapid, reliable widefield MERFISH imaging in 30-μm-thick tissue sections, three times thicker than conventional workflows, with transcripts resolved across z-planes for continuous three-

dimensional reconstruction of intact tissue volumes using standard widefield instrumentation. Together, these advances improve the robustness, sensitivity, and scalability of MERFISH while remaining compatible with existing workflows, enabling more reliable spatial transcriptomic analysis of complex tissues.



Disclosures: Z. Starr: None. **Q. Feng:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.06/II27

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

Support: NIH Grant UM1MH130981

Title: Toward community annotation of a cross-species, spatial transcriptomic atlas of the thalamus

Authors: *M. A. TURNER[1], M. N. HEWITT[1], S. C. SEEMAN[1], D. MCMILLEN[1], C. S. KIM[1], N. MARTIN[1], P. OLSEN[1], S. RANSFORD[1], N. VALERA CUEVAS[1], J. WATERS[1], S. BARTA[1], A. RUIZ[1], J. ARIZA TORRES[1], K. LEVANDOWSKI[3,4], D. YUAN[1], I. KAPEN[2], A. GARCIA[2], K. SMITH[1], L. CACERES[5], J. SCHEMBRI[5], S. DAN[5], M. DEBERARDINE[5], G. FENG[3,4], F. M. KRIENEN[5], R. D. HODGE[2], Z. YAO[1], N. JOHANSEN[2], H. ZENG[1], E. LEIN[2], B. R. LONG[1];
[1]Brain Sci., [2]Brain Hlth., Allen Inst., Seattle, WA; [3]Brain and Cognitive Sci., MIT, Cambridge, MA; [4]Stanley Ctr. for Psychiatric Res., Broad Inst. of MIT and Harvard, Cambridge, MA; [5]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Our understanding of thalamocortical circuits in human and non-human primates can be enhanced by a comprehensive characterization of transcriptomically defined cell types in the thalamus. While such detailed transcriptomic profiling has enabled access to precise cell populations in the mouse thalamus via genetic tools, analogous cell type annotations and access are lacking in primates. As part of the NIH BRAIN Initiative Cell Atlas Network (BICAN), we

are assembling atlases that define a unified framework for transcriptomic cell types across human, macaque, marmoset, and mouse brains. As one piece of this whole-brain effort, we present the current state of the transcriptomic taxonomy in the thalamus and adjacent regions (habenula, zona incerta). We integrated new human and non-human primate single-nucleus RNA-seq data with published mouse single-cell RNA-seq datasets, aligning thalamic cell types and harmonizing nomenclature across human, macaque, marmoset, and mouse. We grounded these cell type identities in anatomy by performing cellular-resolution spatial transcriptomics in the macaque and marmoset, using the Xenium platform to sample across the full anterior-posterior extent of the thalamus in both species. We then linked these anatomically anchored cell types back to published mouse MERSCOPE datasets, allowing us to identify thalamic nuclei that are defined by discrete organization of cell types and those that are characterized by spatially variable gene expression gradients across species. The success of this atlas depends on community adoption and linking its transcriptomic cell types to prior literature on thalamic organization, function, and circuits. To this end, we welcome and encourage external feedback and expert opinions by engaging interested members of the thalamus community via a cell type annotation working group.

Disclosures: M.A. Turner: None. **M.N. Hewitt:** None. **S.C. Seeman:** None. **D. McMillen:** None. **C.S. Kim:** None. **N. Martin:** None. **P. Olsen:** None. **S. Ransford:** None. **N. Valera Cuevas:** None. **J. Waters:** None. **S. Barta:** None. **A. Ruiz:** None. **J. Ariza Torres:** None. **K. Levandowski:** None. **D. Yuan:** None. **I. Kapen:** None. **A. Garcia:** None. **K. Smith:** None. **L. Caceres:** None. **J. Schembri:** None. **S. Dan:** None. **M. DeBerardine:** None. **G. Feng:** None. **F.M. Krienen:** None. **R.D. Hodge:** None. **Z. Yao:** None. **N. Johansen:** None. **H. Zeng:** None. **E. Lein:** None. **B.R. Long:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.07/II28

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

Support: Roy. J. Carver Charitable Trust #25-6023
NIH BRAIN Initiative Armamentarium UF1MH128336

Title: Spatial multiplexed profiling of microRNAs in intact mouse brain

Authors: *H. LI[1], M. JANG[2,3,4,5];
[1]university of illinois urbana-champaign, Champaign, IL; [2]Bioengineering, [3]Neurosci. Program, [4]Carl R. Woese Inst. for Genomic Biol., [5]Beckman Inst. of Advanced Sci. and Technol., UIUC, Urbana, IL

Abstract: MicroRNAs regulate neuronal identity, maturation, and gene expression, yet their spatial distribution within intact brain tissue remains difficult to measure. Although spatial

transcriptomics has enabled tissue-scale gene expression analysis, most workflows are optimized for mRNAs or polyadenylated transcripts and are not well suited for short, non-polyadenylated RNAs, such as miRNAs. Spatially resolved miRNA profiling remains an emerging area, and improved methods are needed to preserve, amplify, and detect miRNA signals in a tissue context. To address this, we developed a new imaging-based method for spatially resolved, multiplexed miRNA detection in thick mouse brain tissue. Previously, we developed ultrasensitive sequential fluorescence in situ hybridization (USeqFISH) that enables then detection of transcripts as short as 40-nt in intact thick tissue, and we have further improved the method to be applicable for ~20-nt transcripts (USeqFISH for non-coding RNAs: nc-USeqFISH). We applied this workflow to mouse brain sections, confirming multi-color detection of well-established miRNAs including miR-124, miR-128, and miR-10 with high specificity. We also optimized the tissue clearing protocol, enabling miRNA detection in >100 um-thick tissue. In addition to multiplexed miRNA detection in deep tissue, we show simultaneous detection of miRNA with mRNAs in the same tissue, demonstrating the feasibility of co-profiling both coding and non-coding RNAs. Ongoing experiments include scaled miRNA mapping by adapting sequential imaging (>50 targets) and temporal barcoding (>500 targets) in the intact mouse brain. By adapting USeqFISH for small noncoding RNA detection, this workflow enables multiplexed spatial miRNA profiling in thick brain tissue and provides a foundation for mapping miRNA-mediated gene regulation within intact brain architecture.

Disclosures: H. Li: None. **M. Jang:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.08/II29

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

Support: Roy. J. Carver Charitable Trust #25-6023
NIH BRAIN Initiative Armamentarium UF1MH128336

Title: Machine-Guided Probe Selection for Single-Probe Transcriptomics using USeqFISH

Authors: *A. CHAUHAN[1], E. HOLMES[2], M. LAWSON[3], M. JANG[1,4,5,6];
[1]Bioengineering, [2]Neural Engin., [3]Material Sci. and Engin., [4]Neurosci. Program, [5]Carl R. Woese Inst. for Genomic Biol., [6]Beckman Inst., Univ. of Illinois Urbana-Champaign, Urbana, IL

Abstract: Fluorescence in situ hybridization enables direct visualization of RNA molecules in cultured cells and intact tissues while preserving spatial information lost in dissociative transcriptomic methods. However, its detection sensitivity depends on efficient probe hybridization. USeqFISH is a recently developed approach that generates bright fluorescent signals from individual transcripts using a single probe, reducing the need for multiple probes per target gene. Despite this advantage, identifying high-performing probe sequences remains a

major challenge because hundreds of candidate probes can be designed for a transcript, yet only a subset produce strong and specific signals. We hypothesized that the probe sequence contains sufficient information to predict probe performance in USeqFISH. Recent advances in genomic machine learning (ML) have shown that nucleotide sequences encode predictive features linked to diverse experimental readouts, including gene expression and chromatin accessibility. These findings suggest that USeqFISH probe performance may also be predictable from sequence-derived features.To generate a training dataset, we designed and tested 171 candidate probes targeting three housekeeping genes (Actb, Pgk1, Polr2a). Confocal images were acquired following USeqFISH labeling, and an image-analysis pipeline was developed for cell segmentation and fluorescent spot detection. Probe performance was quantified as spot count per cell. Probe sequences were represented using one-hot encoding, and transcript position was included as an additional feature. Three gradient-boosted decision tree models (LightGBM, CatBoost, and XGBoost) and a convolutional neural network (CNN) were trained using probes from Actb, Pgk1, and Polr2a and evaluated on previously unseen Tfrc probes.Model performance was assessed using normalized discounted cumulative gain (NDCG), comparing predicted probe rankings with experimentally determined rankings based on spot counts. CatBoost achieved the highest performance among the tree-based models (NDCG = 0.913), while the CNN achieved an NDCG of 0.925 on 60 Tfrc probes. Combining CatBoost and CNN rankings further improved performance, yielding a cumulative NDCG of 0.95 and correctly identifying the highest-performing probe.These results demonstrate that USeqFISH probe performance can be predicted from sequence-derived features using ML. This data-driven framework provides a scalable strategy for prioritizing high-efficiency probes and will facilitate large-scale single-probe spatial transcriptomic profiling.

Disclosures: A. Chauhan: None. **E. Holmes:** None. **M. Lawson:** None. **M. Jang:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.09/II30

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

Title: Random Priming Enables Discovery-Driven, Whole-Transcriptome Spatial Analysis of FFPE Tissues

Authors: *C. XIA, C. R. UYTINGCO, J. WILHELMY, **A. BARRETT**, J. SAKKOS, T. HUI, A. SHAHRAVAN, D. KOOL, W. WANG, B. BELL, C. CHANG, C. FAN;
Takara Bio USA, Inc., San Jose, CA

Abstract: Spatial transcriptomics technologies have been widely used to resolve gene expression within the native tissue environment, transforming our understanding of how cells organize and function in the brain under both healthy and diseased conditions. However, broad adoption is constrained by tissue compatibility: FFPE is the most widely used preservation method, yet the

chemical modifications it introduces compromise RNA integrity, forcing most FFPE-compatible spatial platforms to rely on targeted, probe-based approaches that limit discovery-driven research. These methods work by hybridizing target-specific probes directly to RNA within the tissue — an approach that tolerates degraded RNA but anchors detection to a predefined gene panel, restricting species support and precluding detection of mutations, isoforms, and non-coding RNAs.
To address these limitations, we combined the Trekker technology with a workflow that uses random priming to increase the detection sensitivity of degraded RNA. Following in situ random priming, a poly(A) tail is added to the newly synthesized cDNA, serving as a universal binding site for standard, oligo(dT)-capturing downstream single-cell platforms. The tissue is then spatially tagged with a bead array that contains photo-cleavable barcodes, and dissociated into single nuclei for capture on any dT based single-cell platform. This workflow enables discovery-driven, whole-transcriptome spatial analysis at true single-cell resolution, without the need for cell segmentation or deconvolution. To our knowledge, this is the first FFPE-compatible spatial transcriptomics method to achieve this combination. We validated this approach across three single-cell platforms, including Illumina Single Cell 3', BD Rhapsody, and 10x Genomics 3', and successfully applied the technique to both mouse and rat FFPE brain samples. The workflow detected dozens of neuronal and non-neuronal cell types and resolved their spatial distributions. Furthermore, we extended our analysis to the spatial distribution of isoforms and non-coding RNAs, both inaccessible to probe-based methods. Given the ubiquity of FFPE across research biobanks, pathology archives and clinical collections, this technique opens previously intractable sample types to spatially resolved, single-cell whole-transcriptome analysis across basic neuroscience, translational research and clinical pathology.

Disclosures: C. Xia: A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **C.R. Uytingco:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **J. Wilhelmy:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **A. Barrett:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **J. Sakkos:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **T. Hui:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **A. Shahravan:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **D. Kool:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **W. Wang:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **B. Bell:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **C. Chang:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC. **C. Fan:** A. Employment/Salary (full or part-time):; I am an employee of Takara Bio USA, Inc. USA, INC..

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.10/II31

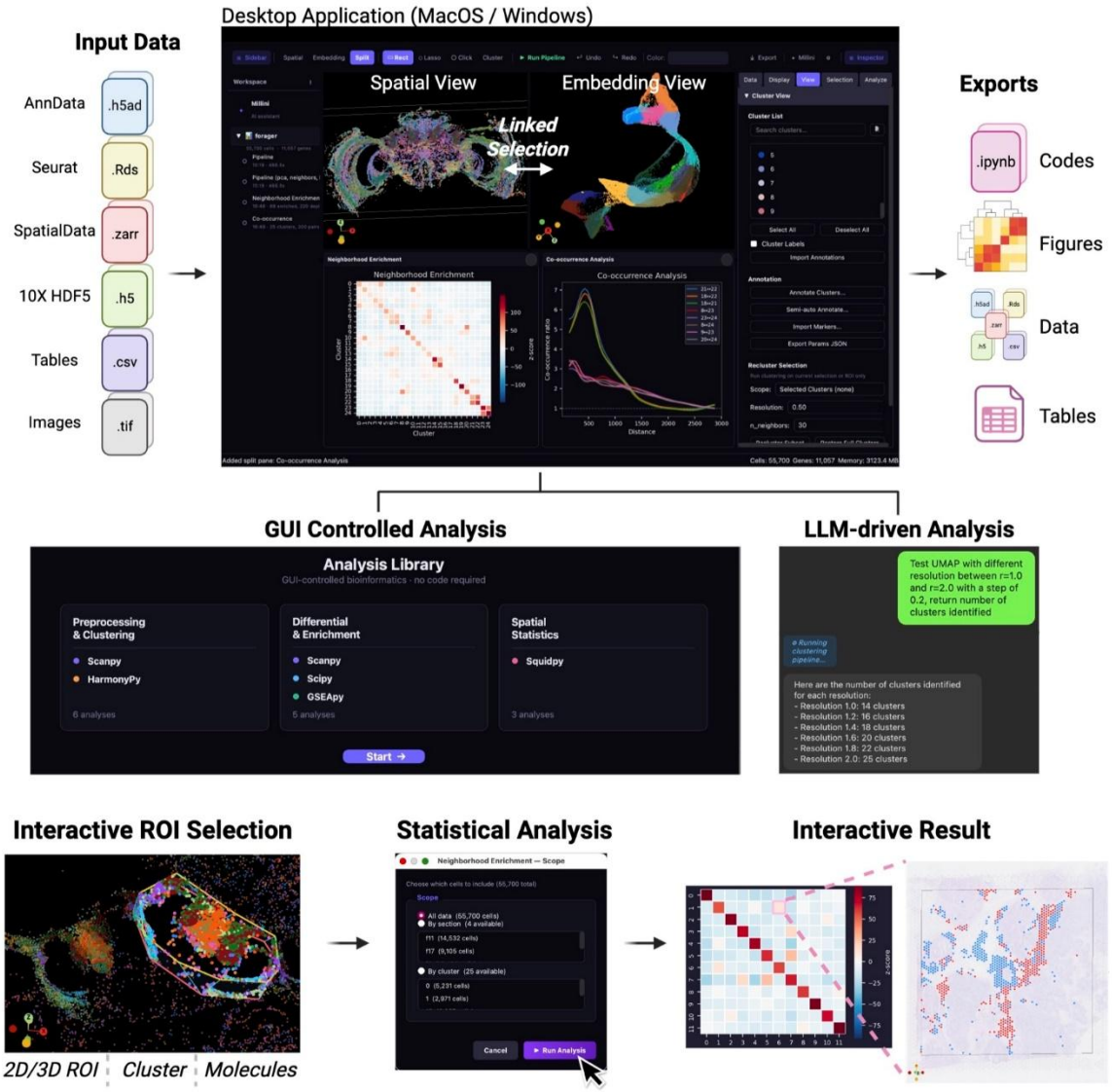
Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R35GM147420

Title: MilliMap: interactive closed-loop spatial omics analysis with applications to behavioral specialization in the honey bee brain

Authors: *Q. FENG[1], S. ASIF[2], Z. STARR[3];
[1]Univ. of Illinois Urbana-Champaign Neurosci. Grad. Program, Champaign, IL; [2]Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Chem., Univ. of Illinois Urbana-Champaign, Hinsdale, IL

Abstract: Spatial transcriptomics is rapidly expanding our ability to map molecules within intact tissues, providing new insight into development, behavior, and disease. However, increasingly complex spatial datasets remain difficult to interpret, requiring fragmented tools across visualization, analysis, and biological interpretation. As spatial transcriptomic and proteomic datasets grow in scale and complexity, extracting biologically meaningful patterns timely has become a major bottleneck. To address this challenge, we developed MilliMap, an interactive closed-loop framework that unifies spatial transcript- and prote-omics visualization, analysis, and interpretation within a single environment (Fig. 1). MilliMap introduces three conceptual innovations: (1) bidirectional linkage of spatial and embedding views for visually guided analysis; (2) GUI- and AI-assisted execution of built-in analytical workflows; and (3) transformation of static analytical outputs into interactive exploratory interfaces linked to spatial context. We applied MilliMap to spatial transcriptomic datasets from soldier and forager honey bee brains, a model system for behavioral specialization. Although worker bees share similar genetic backgrounds and morphology, they exhibit striking differences in aggression and task-associated behaviors. Previous studies identified colony-level aggression-associated genes and phenotypic gene regulatory networks, yet their spatial organization within the brain remains poorly understood. Using MilliMap, we identified phenotype-associated differential spatial expression patterns, hotspots enriched for neurotransmitter receptors, and regional molecular signatures associated with behavioral states. Together, we demonstrate how MilliMap accelerates biological discovery from complex spatial omics datasets while revealing spatial organization of behavioral phenotypes in the honey bee brain. MilliMap establishes a scalable framework for interactive, AI-assisted spatial omics analysis across diverse biological systems.



Disclosures: Q. Feng: None. **S. Asif:** None. **Z. Starr:** None.

Poster

PSTR113: Genomic and Transcriptomic Techniques (Non-Human)

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR113.11/II32

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

Title: A Novel Approach for Spatial Analysis of Microglia in AD Mouse Brain

Authors: *B. TIPTON[1], H. T. YORK[2], C. ZURHELLEN[1], J. BAUN[3];
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Abstract: A Novel Approach for Spatial Analysis of Microglia in AD Mouse Brain
A common approach to analyzing pathology in Alzheimer's Disease (AD) mouse brains is quantifying plaque burden, either through densitometric quantification or counting plaques. Additionally, the relationship between plaques and surrounding cell populations is routinely studied. For AD brains, a common immunofluorescence stain combination is A-beta 1-42 to stain amyloid plaques and Iba1 to stain microglia for inflammation. The antibody combination will vary depending on what endpoints the researcher wants to achieve. Densitometry is sufficient in producing accurate signal area and percent area readouts; however, another method can be used to provide further understanding of the ongoing pathology in AD mouse brains.Spatial analysis uses accurate count of cells in relation to the center of the amyloid plaques. Congo Red dye is used to stain the amyloid plaque core and PU.1 is used to stain the nucleus of microglia. With this combination of stains, one can accurately count the number of microglia surrounding the amyloid plaques and the distances of the microglia from the plaques; revealing a novel aspect of AD pathology not commonly observed. This same method can be achieved with additional readouts in multi-channel immunofluorescent staining to highlight dense plaque cores, total plaque area, along with microglia proximal to plaques.

Disclosures: B. Tipton: None. **H.T. York:** None. **C. Zurhellen:** None. **J. Baun:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.01/JJ1

Topic: J.03. Anatomical Methods

Support: Estonian Research Council PRG2145

Title: 3D Image Analysis for Removing Artifactual Signals: Evaluating Fluorescent Tag Non-Specificity for Peroxisomes in Fixed Neuronal Somas and Axons

Authors: *L. TAMMSAAR-MEUS, D. SAFIULINA, A. KAASIK;
Univ. of Tartu, Tartu, Estonia

Abstract: BACKGROUND. Fluorescent tags, such as mCherry and EGFP, are widely used in functional microscopy experiments. Spherical organelles, such as peroxisomes, lysosomes, endosomes, and autophagosomes, are difficult to distinguish in microscopy images based solely on size. Since a fluorophore is a foreign body to the cell, there is reason to believe that cells degrade them via auto- and lysosomes just as actively as they do old and defective organelles. **OBJECTIVES.** To assess the specificity of fluorescent tags in fixed neurons, focusing on peroxisomes in the soma and axons. To develop a 3D analysis methodology that reduces the

misinterpretation of false-positive and false-negative values. **MATERIALS AND METHODS.** Using Lipofectamine™ 2000, cortical neurons from Wistar rat pups (P0-1, mixed sex) were transfected at 2 days *in vitro* (DIV) with three plasmids to visualize peroxisomes (PTS1), autophagosomes (LC3), and lysosomes (LAMP1). During the experiments, combinations of fluorescent tags (mCherry2, mCitrine, YPet, mTurquoise2) attached to the organelle proteins were varied. As a control, identical combinations of fluorescent tags were used, substituting the peroxisomal marker with cytosolic marker. At 5 DIV, the cells were fixed (4% paraformaldehyde), and 3D imaging (n=10-12 neurons across 3 independent cultures) was performed using a Zeiss LSM 980 confocal microscope. Lateral and axial shifts were corrected using Zeiss Zen 3.13 (blue) software, followed by a 3D intensity analysis using Arivis Vision 4D. Microsoft Excel 365 and GraphPad Prism 9 were used for data analysis. Different receiver operating characteristic (ROC) analysis methods (Youden, Euclidean, IU, Product) were tested and applied to differentiate between false-positive and false-negative values. **RESULTS AND CONCLUSIONS.** Widely used fluorescent tags for peroxisomes are not entirely specific. Preliminary data suggest that true peroxisomes constitute only about 10% of the visualized structures in the mid-axon, and approximately 95% in the soma. The remaining false-positive signals are located in auto- and lysosomes, reflecting pexophagy and the degradation of fluorophores. The artifactual nature of these signals is also evidenced by fluorescently tagged cytosolic markers, which exhibit similar fluorescent structures in auto- and/or lysosomes. The non-specificity of fluorescent proteins is further confirmed by experiments involving other organelles and proteins. The developed 3D image analysis methodology allows for the removal of artifactual signals from the intensity values obtained through automated analysis, significantly increasing the reliability of the data.

Disclosures: L. Tammsaar-Meus: None. **D. Safiulina:** None. **A. Kaasik:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.02/JJ2

Topic: J.03. Anatomical Methods

Support: NIH GM144308

Title: Analyzing Usage Metrics of Problematic Antibodies: Do Authors Act on Warnings Visible in the RRID Portal?

Authors: A. DEWITT[1], D. HOVAKIMYAN[2], A. ASDOURIAN[3], *A. E. BANDROWSKI[4]; [1]Neurosci., UCSD, La Lolla, CA; [2]UCSD, Porter Ranch, CA; [3]UCSD, LA JOLLA, CA; [4]UCSD, La Jolla, CA

Abstract: The RRID, Research Resource IDentifier, Portal (RRID:SCR_004098) was officially launched in 2014 in order to improve the transparent representation of research resources such as

antibodies in the scientific literature. One aspect of the RRID portal is the ability to attach information about the quality of a reagent, and we previously showed that these tags are an effective means to reduce usage of problematic cell lines Babic, et al. 2019 (PMID:30693867). In 2020, we enabled issue tags for antibodies and added a set of tags about the lack of specificity for some antibodies (training data from Hsu et al, 2020; PMID:34043624). However, we do not know if antibody issue tags reduce the usage of antibodies. To study this question, we identified 5 primary antibodies with over 100 citations that had a "non-specific" issue tag. As a control, we looked at PubMed Central citations of the same antibodies without the use of RRIDs, i.e., manuscripts in which the antibody was cited by catalog number and vendor name. We plotted the counts of antibody papers per year, found the best fit line, and examined the average slope of the control group (antibodies where authors did not use RRIDs) and compared the average slope of the experimental group before the issue tag and after the issue tag. The slopes after the issue tag were lower than controls and lower than pre-issue tag in 3 of 5 antibodies. We will examine additional controls to determine if there were other factors in the antibody literature that might account for the reductions in the RRID usage slope that could account for the data. These findings suggest that issue tags alone reduced the use of some problematic antibodies but not in a consistent manner.

Disclosures: A. DeWitt: None. **D. Hovakimyan:** None. **A. Asdourian:** None. **A.E. Bandrowski:** A. Employment/Salary (full or part-time):; SciCrunch Inc., Co-Founder CEO.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.03/JJ3

Topic: J.03. Anatomical Methods

Title: Mapping structural dynamics of neural networks with super-resolution multicolor imaging

Authors: *Y. WANG[1], Y. ZHANG[2], L. YE[1], K. WANG[3];
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Abstract: Dendritic spines undergo rapid structural dynamics in the brain. Spine dynamics are crucial physiological processes regulated by multiple factors, including surrounding neurons, glial cells, and the extracellular matrix. Due to limitations in resolution, previous studies mainly focused on spine turnover. Super-resolution microscopy can potentially reveal these dynamics in much greater detail but has been challenging in behaving animals because of severe motion artifacts. In addition, because available fluorescent protein spectra are limited, it is hard to image multiple component interactions at the same time.Here, we report a multi-color, multiplexed line-scanning structured illumination microscope (MLS-SIM) that achieves 150 nm lateral resolution. MLS-SIM performs super-resolution imaging in all three dimensions within a single

continuous scan of multiplexed and patterned line excitations. In this way, it can tolerate severe sample motion of up to ~50 μm/s. We demonstrated the capabilities and robustness of MLS-SIM by imaging and tracking morphological dynamics in dendritic spines and axonal boutons over hundreds of time points. Furthermore, using spectral imaging, we are able to separate fluorescent proteins that have similar emission spectra—for example, GFP and YFP, both excited only by the 488 nm laser line. With the 488, 561, and 635 nm laser lines, we can simultaneously image up to four channels. Using this method, we directly visualized interactions between dendritic spines and other neurons, glial cells, and the extracellular matrix, demonstrating that multi-color MLS-SIM can map structural dynamics of neural networks at super-resolution and reveal the relationship between in vivo spine dynamics and local microenvironment interactions.

Disclosures: Y. Wang: None. **Y. Zhang:** None. **L. Ye:** None. **K. Wang:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.04/JJ4

Topic: J.03. Anatomical Methods

Support: Howard Hughes Medical Institute

Title: An average Mus brain doesn't exist but we made one anyway

Authors: *N. SHETTIGAR[1], B. FOSTER[1], I. SIWANOWICZ[1], M. COPELAND[1], P. CONWAY[2], T. J. RYAN[2], A. E. COMRIE[1], J. VOIGTS[1], G. IHRKE[1], N. IYER[1], E. J. DENNIS[1];
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Abstract: Stereotaxic atlases are foundational to targeting brain regions for neuroscience, yet nearly all mouse references derive from one inbred strain, C57BL/6J. Coordinates do not transfer reliably across strains, and divergence grows across the genus Mus, where brain size, regional proportions, and brain-to-skull geometry differ substantially (Wahlsten et al. 1975). Yet these Mus species and subspecies are increasingly valuable as models precisely because they diverge behaviorally from standard laboratory strains, displaying distinct social, reproductive, and ecological repertoires shaped by their natural histories (Fonio et al. 2006). Studying the neural basis of such natural behaviors demands accurate, species-specific targeting that current atlases do not provide. We have built species-specific, computational, stereotaxic atlases by combining two modalities: light-sheet imaging and microCT. For brain maps, whole brains are cleared with iDISCO, imaged intact by light-sheet microscopy, and iteratively aligned and averaged into an annotated population template (a "common coordinate framework"). For stereotaxic maps, intact heads are stained and imaged by microCT to localize bregma, lambda, and other landmarks in relation to brain structures. Co-registering the two yields a complete, computational, stereotaxic

atlas per taxon. As an example, we present an averaged Mus caroli brain template built from 8 cleared, light-sheet-imaged brains and identify key differences between Mus caroli and Mus musculus. We demonstrate the utility of this approach across multiple Mus species and subspecies including M. caroli, M. spicilegus, M. spretus and both laboratory and wild-derived Mus musculus. Together these data and methods reveal new biological insights and reduce the number of animals needed for targeting brain regions across species by establishing accurate, species-aware stereotaxic atlases.

Disclosures: N. Shettigar: None. **B. Foster:** None. **I. siwanowicz:** None. **M. copeland:** None. **P. Conway:** None. **T.J. Ryan:** None. **A.E. Comrie:** None. **J. Voigts:** None. **G. Ihrke:** None. **N. Iyer:** None. **E.J. Dennis:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.05/JJ5

Topic: J.03. Anatomical Methods

Support: DCIDDRC P50HD105328

Title: Volumetric Reconstruction of GABAergic Synapses using Post-embedding Immunogold in Serial Sections

Authors: *S. GARCIA-HERNANDEZ[1], C. CLARKSON[2], A. POPRATILOFF[3];
[1]The George Washington Univ., Washington, DC; [2]George Washington Univ., Washington, DC, ; [3]Anat. and Regenerative Med., George Washington Univ., Washington, DC

Abstract: Post-embedding immunogold (PI) is a unique method to label specific antigens while preserving ultrastructural details of subcellular structures. PI labeling is broadly used in neuroscience research to locate and quantify specific molecules within neuronal compartments. This technique has been extensively applied with transmission electron microscopy (TEM) to analyze only a few serial sections, due to the x-y restrictions. In the past decade, high-resolution backscatter scanning electron microscopy (bSEM) has been employed to produce images that are comparable in quality to those obtained with TEM, with the advantage of capturing dozens to hundreds of serial sections simultaneously over larger areas. To our knowledge, no studies have combined bSEM and PI to label neurochemical molecules within a three-dimensional (3D) microcircuit to understand its functional connections. As a proof of principle, we used PI in serial sections and bSEM to assess the subcellular localization and quantity of gamma-aminobutyric acid (GABA), a major neurotransmitter in the brain. 2D images were aligned and registered in Amira software to create 3D reconstructions, which were segmented and visualized in Imaris software. Gold particles were segmented using the spot detection model of Imaris, based on the intensity profile of 3D images. Synaptic terminals and dendrites were manually segmented, and gold particles within terminals were isolated via spatial association. This

workflow demonstrates that post-embedding immunogold has the sensitivity to detect varying densities of GABA in synaptic terminals, without losing ultrastructural details after immuno-labelling. The use of bSEM enables the scanning of large areas while maintaining high resolution, important for interpreting data within an anatomical context. Volumetric reconstructions and segmentation of synaptic terminals in the mouse brainstem were consistent in identifying both GABAergic and non-GABAergic terminals as well as their spatial interactions. This approach enhances our understanding of functional connections in the spinal trigeminal nucleus.

Disclosures: S. Garcia-Hernandez: None. **C. Clarkson:** None. **A. Popratiloff:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.06/JJ6

Topic: J.03. Anatomical Methods

Support: NIH Grant R01MH132544

Title: Unlocking archival human brain tissue for electron microscopy

Authors: *M. MAIER, J. DURBIN, J. KOZEL, J. R. GLAUSIER;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Investigating cellular, organelle, and synaptic function in human brain is essential for determining the mechanisms underlying neurologic and psychiatric disorders. Electron microscopy (EM) analyses of ex vivo postmortem human brain tissue provide a window into in vivo function, as ultrastructural features of synapses and mitochondria have been shown to reflect synaptic efficacy, metabolic state, and local circuit organization in model systems and, more recently, in postmortem human cortex. However, widespread application of EM to archival human tissue is limited by fixation chemistry: many banked specimens are fixed in 4% paraformaldehyde (PFA), which preserves gross morphology but may not adequately stabilize membranes for high-resolution ultrastructural analysis. We therefore developed a workflow to rescue archival PFA-fixed postmortem human dorsolateral prefrontal cortex for EM. Post-fixation conditions were systematically compared using glutaraldehyde (GA), tannic acid, and reduced osmium strategies, followed by en bloc heavy metal staining, resin embedding, and evaluation by transmission EM for cell and organelle membrane preservation, mitochondrial morphology, synaptic vesicle pool definition, postsynaptic density visibility, and overall neuropil quality. A post-fixation mixture of 0.2% GA and 2.5% potassium ferrocyanide yielded clearly resolved cell and organelle membranes, synaptic vesicle pools, postsynaptic densities, and mitochondrial profiles. This leading condition was then advanced to focused ion beam-scanning electron microscopy, where it supported volume acquisition and automated three-dimensional mitochondrial detection and segmentation using napari-empanada. These findings provide proof

of concept that archival PFA-fixed human brain tissue can be adapted for EM and further validated by volumetric imaging, expanding the utility of existing brain bank resources for quantitative studies of cellular, organellar, and synaptic pathology in human disease.

Disclosures: M. Maier: None. **J. Durbin:** None. **J. Kozel:** None. **J.R. Glausier:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.07/JJ7

Topic: J.03. Anatomical Methods

Support: NSERC - RGPIN-2018-06506
NSERC - DGECR-2021-00228

Title: Histological and MRI Characterization of the Basal Ganglia in Human Brains Fixed with Gross Anatomy Laboratory Solutions

Authors: *V. PERREAULT[1], E.-M. FRIGON[1,2], M. DADAR[3], D. BOIRE[1], J. MARANZANO[1,4];
[1]Dept. of anatomy, Univ. of Québec in Trois-Rivières, Trois-Rivières, QC, Canada; [2]Douglas Res. Center, McGill Univ., Montréal, QC, Canada; [3]Biomed. Engin., McGill Univ., Montreal, QC, Canada; [4]Dept. of Neurol. and Neurosurg., Montréal Neurolog. Institute, McGill Univ., Montréal, QC, Canada

Abstract: Research using ex vivo human brains generally relies on brain banks that provide small tissue samples fixed by immersion in neutral buffered formalin (NBF), while gross anatomy laboratories could provide whole brain samples. However, they use whole body perfusion with solutions optimized for dissection, like an alcohol-formaldehyde solution (AFS). Consequently, AFS-fixed brains may exhibit characteristics that differ from those of NBF-fixed brains and require further assessment and comparison. Magnetic resonance imaging (MRI) is a non-invasive imaging modality that allows the visualisation of tissue contrasts. Because ex vivo scans are limited by their macroscopic resolution, MRI findings must be confirmed using gold standard histology. Our previous work demonstrated the feasibility of multiple histochemical (HC) and immunohistochemical (IHC) stains, as well as MRI sequences in human neocortical blocks from brains fixed with solutions used in gross anatomy laboratories. However, these approaches have not yet been applied to deeper brain structures, such as the basal ganglia (BG), that may be preserved differently from the neocortex. Therefore, this study aims to compare the BG in AFS- and NBF-fixed brains using histology and MRI. 10 human brain hemispheres fixed with either AFS (perfused; N=5) or NBF (immersed; N=5) were scanned using a 3T MRI to acquire T1- and T2-weighted images, in which the BG were manually segmented using Display (MINC ToolKit). Tissue blocks containing the striatum and globus pallidus were extracted, sectioned at 20 µm using a cryostat, and processed with HC (H&E and cresyl violet) and IHC

staining protocols (anti-NeuN, -ChAT, -DARPP32, -TH, -GFAP, and -Iba1). BG volumes and intensity ratios will be compared between AFS- and NBF-fixed brains. IHC signal will be quantified using intensity-based threshold, whereas ease of manipulation, antigenicity preservation, and HC staining quality will be assessed using qualitative scales. T1- and T2-weighted images provided sufficient grey-white matter contrast to allow manual segmentation of each BG nucleus. Preliminary histological analyses from one AFS- and one NBF-fixed specimen demonstrated feasible staining and good tissue preservation within the BG. This work will establish reliable histology protocols for BG in postmortem human brains fixed in different conditions. This will help determine whether brains obtained from gross anatomy laboratories constitute a suitable alternative to brain bank specimens for neuroscience research using MRI and histological techniques focused on the BG.

Disclosures: V. Perreault: None. **E. Frigon:** None. **M. Dadar:** None. **D. Boire:** None. **J. Maranzano:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.08/JJ8

Topic: J.03. Anatomical Methods

Support: European Union's Horizon Europe Marie Curie grant No. 101270269
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NKKP STARTING_25 grant No. 152117
NKFIH Advanced grant No. 151284
NKFIH EXCELLENCE program grant No. 151377

Title: Angiotensin, cannabinoid and dopamine receptor photoaffinity ligands (PALs) for cell-type- and nanodomain-specific confocal and super-resolution imaging in the brain

Authors: *A. D. TOTH[1,2], S. C. PROKOP[2,4], R. SZABÓ[1], D. KISS[1], L. BARNA[2], B. BARNA[5], D. LESZKÓ[4], D. NAGY[4], M. VÁMOSI[4], A. EGYED[1], P. ÁBRÁNYI-BALOGH[1], L. HUNYADY[1], K. MACKIE[2,3], G. KESERU[1], I. KATONA[2,4];
[1]HUN-REN Res. Ctr. for Natural Sci., Budapest, Hungary; [2]Dept. of Psychological and Brain Sci., [3]Gill Inst. for Neurosci., Indiana Univ., Bloomington, IN; [4]HUN-REN Inst. of Exptl. Med., Budapest, Hungary; [5]Imperial Col. London, London, United Kingdom

Abstract: Fluorescent ligands are powerful complements to antibodies for high-resolution visualization of cell-surface receptors, as demonstrated by our recently developed PharmacoSTORM probes[1]. However, their application to tissue imaging has remained limited. We found that rapid probe dissociation from receptors is the key bottleneck to broader

applicability, because it reduces the stability of fluorescent ligand-based receptor labeling and hinders compatibility with time-consuming imaging and antibody-based protocols. To overcome this limitation, we developed PharmacoSTORM2.0 probes: Sulfo-Cy5-labeled receptor ligands equipped with a UV-activatable photoaffinity group. These probes retain the pharmacological selectivity of ligand-based labeling and dissociate from their receptors without UV illumination. Conversely, UV exposure converts the interaction into a covalent linkage, thereby stabilizing the ligand-receptor complex. Here, we introduce photoaffinity ligands (PALs) for three pharmacologically relevant G protein-coupled receptors: the cannabinoid CB_1 receptor, the dopamine D_1 receptor, and the angiotensin II type 1 receptor, termed CB_1-PAL, D_1-PAL, and AT_1-PAL, respectively. In addition, we provide an efficient workflow for photoaffinity labeling in cultured cells and in *ex vivo* mouse hippocampus, hypothalamus and striatum acute slice preparations. We demonstrate successful application of these probes across multiple light-microscopy modalities, including epifluorescence, confocal, and STORM super-resolution microscopy. The approach enables the quantitative visualization and measurement of ligand-accessible receptor pools at regional, cellular, and subcellular levels even for targets for which selective antibodies are unavailable. In summary, PharmacoSTORM2.0 provides a versatile approach to map the spatial organization of drug-accessible receptors in brain circuits in a cell-type-specific manner and with nanoscale precision.

[1]Prokop S. *et al.* Nat Commun. 2021

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Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.09/JJ9

Topic: J.03. Anatomical Methods

Support: RS-2021-NR056586

Title: Organism-Scale Molecular Circuit Mapping Using Expansion Microscopy and Multiplexed Imaging

Authors: W. LA[1], J. KIM[2], ***J.-B. CHANG**[2];
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Abstract: Understanding how molecular identity is organized across long-range neural circuits remains a central challenge in connectomics. Electron microscopy provides ultrastructural detail, while fluorescence microscopy offers molecular specificity; however, achieving nanoscale resolution, organism-scale coverage, and high-dimensional molecular profiling within a single imaging framework remains difficult. In this poster, we present our efforts toward molecular whole-body connectomics by integrating expansion microscopy with multiplexed imaging. We will discuss four directions: expansion methods that enlarge biological specimens by more than fourfold to enable sub-20-nm-resolution imaging; the application of expansion microscopy to whole vertebrate bodies, extending super-resolution imaging beyond isolated organs or tissue sections to the scale of the entire organism; multiplexed imaging approaches for unexpanded specimens that visualize more than 30 proteins in the same sample and characterize molecular heterogeneity; and strategies for combining multiplexed imaging with expansion microscopy. Together, these advances outline a technical framework for mapping morphology, molecular identity, and large-scale anatomical organization across whole organisms, suggesting a path toward molecular whole-body connectomics.

Disclosures: J. Chang: A. Employment/Salary (full or part-time):; Flashomics Corp..

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.10/JJ10

Topic: J.03. Anatomical Methods

Support: NIH/NICHD P50HD105328

Title: GWNIC: A multiscale electron microscopy resource for the neuroscience community. Large-field 2D, 3D SBF, FIB-SEM, CLEM and STEM/ET

Authors: *A. S. POPRATILOFF, S. GARCIA-HERNANDEZ;
George Washington Univ., Washington, DC

Abstract: Volume and large-field electron microscopy (EM) have transformed what can be recovered from any CNS/PNS sample. Still, broad adoption across neuroscience remains limited by narrow fields of view, complex sample preparation, and restricted access to instrumentation. The GW Nanofabrication and Imaging Center (GWNIC) operates an integrated four-modality EM workflow openly available as a national resource: (i) large-field 2D backscattered SEM (bSEM) acquiring cytoarchitectural context at 2-5 nm/pixel using a concentric-backscatter detector for clean elastic-scattering detection; (ii) serial-section bSEM via in-situ mechanical sectioning, producing tile-stitched volumes at 2 nm/pixel XY and 60 nm Z (representative

geometry: acquired in 2 days); (iii) Focused-Ion-Beam SEM (FIB-SEM) at project-appropriate anisotropic or isotropic voxels; and (iv) 200 kV STEM electron tomography (HAADF, high-tilt holder, tilt series in 1° steps over [e.g., ±50°], 0.88 nm pixel, SIRT reconstruction) yielding sub-nanometer isotropic-voxel reconstructions. Sample-preparation throughput is enabled by microwave-accelerated enhanced heavy-metal infiltration, reducing the staining/dehydration/resin cycle from ~2 days to ~3 hours while preserving contrast across tissue types (brains/condition; both sexes; tested on embryonic to adult mouse, primate, and human postmortem tissue). Multi-platform tile registration is unified by navigation/automation software that provides a Google Maps-style zoom path from millimeter-scale context to sub-nanometer voxels within a common coordinate frame. Post-embedding immunogold for neurotransmitters and common receptors has been extended to 3D serial-section registration and to bSEM-compatible workflows on silicon wafers, a capability not currently disseminated by comparator centers. Integrated CLEM workflows (spectral imaging, FLIM, SHG/THG, multiphoton excitation, Airyscan super-resolution) register fluorescence to the same EM coordinates. Representative datasets include hypoglossal motor neuron degeneration in the LgDel model of 22q11.2 deletion syndrome, somatosensory primary afferent volumes, and retinal rod-ribbon synapse tomography.

Disclosures: A.S. Popratiloff: None. **S. Garcia-Hernandez:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.11/JJ11

Topic: J.03. Anatomical Methods

Support: P50HD105328
Siegelman Undergraduate Research Award

Title: Plasma FIB-SEM as an alternative for microcircuit reconstructions: a case study using somatosensory primary afferents in the substantia gelatinosa of the spinal cord

Authors: *T. PATEL[1], V. SUBRAMANIAN[3], D. BUSS[4], C. CLARKSON[2], S. GARCIA-HERNANDEZ[2], A. S. POPRATILOFF[2];
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Abstract: Several approaches to three-dimensional electron microscopy have gained considerable traction over the past decade and are now unified under the term volume electron microscopy. Each carries trade-off. Serial block-face SEM (SBF-SEM) with in-chamber mechanical sectioning has been the most challenging because the cut surface progressively accumulates charge during repeated imaging cycles, with mechanical cutting and electron exposure compounding the problem. Gallium FIB-SEM (Ga-FIB) circumvents charging via the

milled-face geometry, but the imaging plane sits at a fixed tilt of ~38°, complicating co-registration and constraining the lateral field of view (typically ≤ 30 µm). Array tomography with concentric-backscatter (CBS) detection on silicon wafers delivers very large lateral fields but recovery of the third dimension requires extensive elastic alignment. We tested an alternative — the Hydra Bio Plasma FIB-SEM with spin-mill patterning, performed at the Thermo Fisher Nanoport (Hillsboro, OR) — that combines the strengths of these modalities. Positively charged plasma ions counter specimen charging; the spin-mill geometry presents the freshly milled face to the CBS detector over an extended lateral field; three sub-volumes were milled and imaged simultaneously and aligned offline for parallel 3D reconstruction. The workflow was applied to substantia gelatinosa of adult mouse spinal-cord dorsal horn (enhanced heavy-metal staining; epoxy embedding), one of the most challenging cytoarchitectural regions for volume reconstruction. Voxel geometry was 5 × 5 × ~20 nm, each sub-volume ~80 × 80 × 25 µm. Amira AI assisted segmentation and 3D reconstruction discriminated glomerular morphology clearly and recovered C1 terminals — particularly difficult because their fine processes are routinely lost across consecutive sections in other modalities. Co-registration was robust; the lateral field preserved broader laminar context, linking targeted high-resolution sampling to dorsal-horn architecture. Primary-afferent central terminals form synaptic glomeruli — one central terminal contacting multiple dendrites — and were classified as C1, C2, or dense-core-vesicle (DCV)-containing by vesicle composition and surrounding ultrastructure. Single planes could not resolve the multi-dendritic architecture; Plasma FIB-SEM occupies a useful niche between mechanical-sectioning volume EM and Ga-FIB-SEM: lateral surface area approaches that of mechanical sectioning while z-resolution sits at the sweet spot for reliable microcircuit reconstruction.

Disclosures: T. Patel: None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.12/JJ12

Topic: J.03. Anatomical Methods

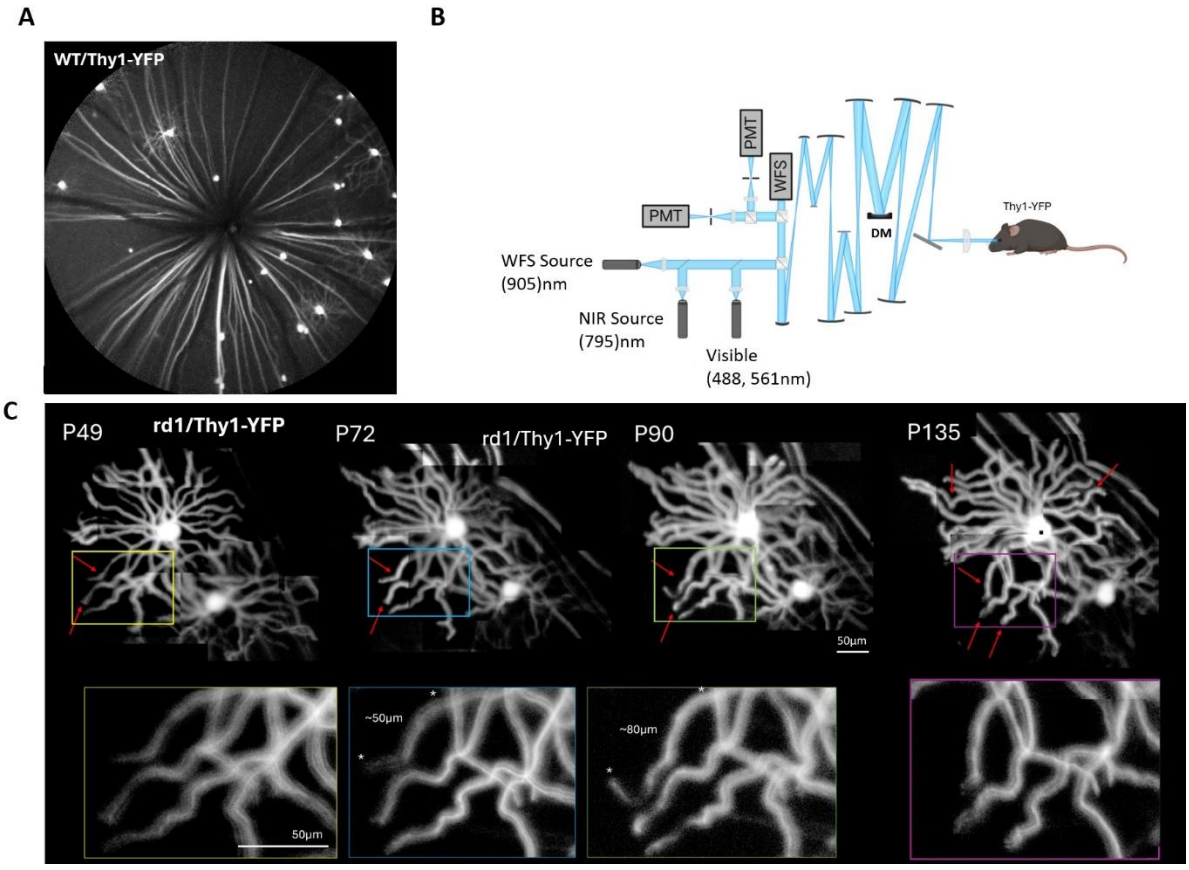
Support: Research to Prevent Blindness, Career Development Award

Title: Longitudinal single-neuron imaging reveals dendritic remodeling of retinal ganglion cells in living mice using adaptive optics scanning laser ophthalmoscopy

Authors: S. BELHADJ[1], D. POWER[3], J. ENDRES[1], J. B. SCHALLEK[3], ***M. TELIAS**[2]; [1]Dept. of Ophthalmology, [2]Ophthalmology, Univ. of Pittsburgh, Pittsburgh, PA; [3]Flaum Eye Inst., Univ. of Rochester, Rochester, NY

Abstract: Neurons dynamically remodel their dendrites in response to changes in stimulation and synaptic input, driving adaptive and pathological plasticity in the nervous system.

Traditional studies rely on post-mortem tissue, providing only snapshots across animals and conditions. In vivo brain imaging approaches are invasive, introduce inflammation, and preclude true longitudinal tracking of the same neuron over time. The retina offers a uniquely accessible window into the nervous system: enclosed within the eye's optics, retinal neurons can be observed directly. Here we present an adaptive optics scanning laser ophthalmoscopy (AOSLO) platform for non-invasive, longitudinal imaging of single retinal ganglion cells (RGCs) in living mice. The complexity and size of the RGC dendritic arbor define its receptive field, and morphological changes imply functional alterations in synaptic integration. We established a colony of Thy1-YFP transgenic mice, in which a sparse subset of RGCs express yellow fluorescent protein, enabling isolation of individual dendritic arbors. A custom AOSLO system corrects ocular aberrations and compensates for retinal motion in real time, achieving diffraction-limited fluorescence imaging at single-micrometer resolution. Individual neurons were re-identified and imaged across four timepoints (P45-135). In WT mice, dendritic arbors remained stable across all sessions, establishing a baseline for platform sensitivity. We then crossed these mice with the rd1 strain, in which photoreceptor loss provides a progressive perturbation to RGC synaptic input, and detected in vivo dendritic remodeling, including extensions and retractions, demonstrating dendritic dynamics associated with retinal circuit breakdown. This paradigm enables the first systematic, longitudinal characterization of RGC dendritic arbor dynamics in a living mammal, allowing precise re-registration of the same neuron across weeks and revealing changes inaccessible to conventional histology.



Disclosures: S. Belhadj: None. **D. Power:** None. **J. Endres:** None. **J.B. Schallek:** None. **M. Telias:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.13/JJ13

Topic: J.03. Anatomical Methods

Title: In vivo two-photon imaging enables cellular-resolution visualization in live tardigrades

Authors: *H. WANG, Y. LIANG;
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Abstract: Tardigrades are emerging model organisms for neuroscience research. They offer a unique platform to investigate mechanisms of neural resilience to extreme stress, with potential implications for neuroprotection in conditions such as stroke and traumatic brain injury. However, tools for cellular-resolution in vivo imaging of their nervous system remain limited. Conventional one-photon wide-field fluorescence microscopy is constrained by poor optical sectioning and substantial out-of-focus background in thick specimens, thereby precluding reliable visualization of neural structures in tardigrades. To address this limitation, we developed a two-photon fluorescence microscopy platform for in vivo imaging of live tardigrades. Tardigrades (Hypsibius exemplaris; Carolina Biological; n = 10 animals across 4 independent experiments) were incubated in 15 μM Hoechst 33342 diluted in 1mL spring water for 20-40 min, washed, and immobilized in low-melting-point agarose within a custom imaging chamber. Imaging was performed using both wide-field fluorescence and two-photon fluorescence microscopy. Acquired images were analyzed in ImageJ. Imaging sessions were limited to 1 h to preserve specimen viability. Wide-field imaging across five channels (polarized light, 405 nm, GFP, Y3, Y5) revealed strong autofluorescence in pharyngeal and head structures, including the buccal tube and stylets, but failed to resolve neural features due to single-plane acquisition and out-of-focus blur. In contrast, two-photon fluorescence microscopy enabled optical sectioning and volumetric imaging via high-resolution z-stacks, allowing visualization of deeper internal structures, including cerebral ganglion regions. At 800 nm excitation, Hoechst-labeled nuclei and endogenous autofluorescence were resolved with cellular and subcellular detail. Optimization of excitation power minimized motion artifacts and improved signal quality. Overall, two-photon microscopy provided superior contrast, depth penetration, and suppression of out-of-focus background compared to wide-field microscopy. These findings establish two-photon fluorescence microscopy as a robust platform for cellular-resolution in vivo imaging of the tardigrade nervous system, enabling future studies of neural circuit structure and function in this emerging model organism.

Disclosures: H. Wang: None. **Y. Liang:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

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Topic: J.03. Anatomical Methods

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SMART-brain project CUP B97G24000240005
FOE 2022- CUP B53C24004790001

Title: Integrated high-speed light-sheet microscopy and LED-mediated autofluorescence suppression for large-scale human brain imaging

Authors: *L. PEREGO[1], D. DI MEO[3], D. NARDINI[1], M. BEDEL[1], F. CARIA[2], S. BRADLEY[1], I. COSTANTINI[3], F. S. PAVONE[4];
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Abstract: Three-dimensional imaging of cleared human brain tissues is increasingly used to investigate cytoarchitecture and neuropathology at cellular resolution. However, large-scale studies remain limited by two major challenges: the need for high-throughput imaging of centimeter-scale specimens and the high levels of endogenous autofluorescence present in adult and pathological human tissues. To address these challenges, we developed a high-speed multiplex light-sheet fluorescence microscopy platform (quad-SPIM) with a tissue-adapted autofluorescence suppression strategy based on controlled LED-mediated photobleaching. Quad-SPIM enables simultaneous four-color acquisition of optically cleared human brain samples at imaging speeds exceeding 3 cm^3/h, corresponding to an approximately 11-fold increase compared with our previous dual-view light-sheet microscope. Human cortical and brainstem tissues labeled with neuronal and myelinated fiber markers were imaged without detectable spectral cross-talk, enabling rapid volumetric reconstruction of centimeter-scale specimens. Comparison with submicronic resolution dual-view acquisitions demonstrated that, for the mesoscopic scale relevant to fiber orientation dispersion analysis, quad-SPIM provides equivalent quantitative information despite lower microscopic resolution, indicating that major gains in throughput can be achieved without compromising biologically meaningful measurements. To further improve image quality, we investigated LED-mediated photobleaching prior to immunolabeling and optical clearing. Autofluorescence reduction was characterized in human brainstem and glioma tissues across multiple spectral channels, revealing distinct tissue-specific photobleaching kinetics. Brainstem tissue requires longer exposure times than glioma to achieve maximal autofluorescence suppression, suggesting differences in endogenous

fluorophore composition. Integration of LED exposure into SHORT- and iDISCO-based workflows substantially reduced autofluorescence and improved signal-to-background contrast in large brainstem and glioma specimens without detectable loss of labeling performance. Together, these results establish an integrated workflow combining high-speed multiplex light-sheet microscopy and tissue-adapted autofluorescence suppression for scalable three-dimensional imaging of healthy and diseased human brain tissues.

Disclosures: L. Perego: None. **D. Di Meo:** None. **D. Nardini:** None. **M. Bedel:** None. **F. Caria:** None. **S. Bradley:** None. **I. Costantini:** None. **F.S. Pavone:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.15/JJ15

Topic: J.03. Anatomical Methods

Support: Fundação Araucária

Title: Xiphoid nucleus: new perspectives from morphological, quantitative and ultrastructural studies of Cocaine and Amphetamine Regulated Transcript (CART) innervation

Authors: *A. SAYURI SENOO KAKUNO[1], C. HAEMMERLE[2];
[1]Federal Univ. of Paraná, Curitiba, PR, Brazil, Londrina, Brazil; [2]Federal Univ. of Paraná, Curitiba, Brazil

Abstract: The Cocaine and Amphetamine Regulated Transcript (CART) is a neuropeptide involved in the modulation of several biological processes, including feeding behavior, fear, addiction, and reward. A fine description on neuroanatomical aspects of CART fibers and their synapsis is useful for supporting the different functions determined in each brain region. A putative new brain area for CART roles is the xiphoid nucleus (Xi), a midline thalamic nucleus recently described as being responsible for the control of food intake in mice exposed to cold environments, as well with the modulation of behaviors related to visual threats. Therefore, the present study aims to: characterize and describe the morphology of Xi neurons; demonstrate the structural and ultrastructural aspects of CART innervation and synapses within the Xi nucleus and compare them to the pattern observed in others midline classical nuclei. For this purpose, the brains of 20 adult male C57BL/6 mice were analyzed. The animals were perfused according to each method to be used: with 0.9% saline solution for Golgi-Cox staining; following with 4% PFA, for histological and immunofluorescence or 4% PFA + 0,1% glutaraldehyde, for ultrastructural studies of immunoreactivity. After post-fixation, the brains were sectioned proceed with according to the lab protocol established. Briefly, the histological studies used Giemsa, Nissl and Golgi-Cox staining protocols. The immunofluorescence study was carried out using rabbit anti-CART polyclonal antibody [1:1000] and anti-rabbit/FITC [1:1000], and analyses were performed using confocal laser microscopy. Finally, the ultrastructural studies of

pre-embedding CART immunoperoxidase were analyzed in transmission electron microscope. The images were evaluated and quantified using Fiji ImageJ software. Our findings show the typical shape of Xi nucleus, clearly contrasting with others midline nuclei. Their neurons are rounded and fusiform. Also, Golgi-Cox staining confirmed typical rounded neurons and the unique pattern of short branching of spiny dendrites. The quantification of immunofluorescence demonstrated that Xi has a high density of ir-CART fibers among other midline nuclei, with a slightly lower density innervation compared to the PVH. Transmission electron microscopy revealed several appositions and synapsis between Xi neurons and CART fibers/terminals. Ongoing functional studies about feeding behavior will confirm the activation of this system. Therefore, we postulate the CART fibers and axons innervating Xi are in position to complement the literature with fine anatomical embasement for the functional roles of Xi nucleus.

Disclosures: A. Sayuri Senoo Kakuno: None. **C. Haemmerle:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.16/JJ16

Topic: J.03. Anatomical Methods

Support: Fundação Araucária
Fapesp
Capes

Title: The immunogold method identifies the ultrastructural aspects of V-SVZ proliferative cells and their synapsis with cocaine and amphetamine regulated transcript (CART)

Authors: *C. A. S. HAEMMERLE[1], A. SAYURI SENOO KAKUNO[3], B. TAQUES MUSSI ENDRES[2];
[1]Anat., [2]Federal Univ. of Paraná, Curitiba, Brazil; [3]Federal Univ. of Paraná, Curitiba, PR, Brazil, Londrina, Brazil

Abstract: The largest niche for neurogenesis in the adult rodent brain is located around the frontal horn of the lateral ventricles. Each different precursor cell involved has its own ultrastructure, as well as a unique potential for entering in the S-phase of the mitotic cycle. Furthermore, this niche is also compartmentalized by a distribution pattern of axonal fibers, such as those carrying the neuroactive peptide CART (cocaine- and amphetamine-regulated transcript), whose description may open perspectives for understanding a putative role of this peptide in the periventricular niche. Therefore, we propose to study the ultrastructure of proliferative cells in the periventricular region and describe the innervation pattern by CART axons. We used adult male C57Bl6 and GFAP:GFP mice. The animals were perfused with different fixatives for subsequent ultrastructural or neurochemical analysis by specific transmission electron microscopy and field-emission scanning electron microscopy, confocal

laser microscopy and light microscopy. To study the progression of cellular proliferation, we administered the antimitotic agent Ara-C, 2%, for 6 days via osmotic mini-pumps. At the end of the Ara-C treatment, the animals received the mitotic cycle marker BrdU (50 mg/kg, i.p.) in a single dose. Immunogold assays were performed using primary anti-BrdU antibodies [1:100] and secondary antibodies conjugated to 0.8 ηm colloidal gold. Immunofluorescence assays were performed using anti-CART, anti-GFAP, anti-DCX, and anti-GFP [1:1000]. High-resolution scanning electron microscopy was used to demonstrate the three-dimensional aspects of the cells. We found that all cell types comprising V-SVZ are BrdU+, with variable densities for each cell class. Neuroblasts exhibit the highest density, while ependymal cells and tanycytes exhibit the lowest density. These cells are also heterogeneous in terms of ciliary distribution density, presenting as uni-, bi-, or multiciliated, and are innervated by varicose axons. Furthermore, the higher density of CART innervation occurs along the migratory path of developing neurons, establishing appositions among primary progenitors, neuroblasts, and BrdU+ cells. Thus, we demonstrate that immunoreactivity to BrdU is observed in all characteristic cellular elements of the periventricular niche, including tanycytes not previously described; there is dense varicose innervation of different ciliated cells and strong fine anatomical evidence suggesting a role for the CART peptide in the regulation of neurogenesis.

Disclosures: C.A.S. Haemmerle: None. **A. Sayuri Senoo Kakuno:** None. **B. Taques Mussi Endres:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

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Program #/Poster #: PSTR114.17/JJ17

Topic: J.03. Anatomical Methods

Support: NIH Grant U01MH114824
NIH Grant U19MH114821

Title: Confocal Airy beam oblique light-sheet tomography for brain-wide cell type distribution and neuronal morphology

Authors: *X. QI[1,2], R. MUÑOZ CASTAÑEDA[5], Y. YUE[7], S. XIAO[8], L. DING[9], A. NARASIMHAN[3], W. WANG[10], Y. LI[11], C. ELOWSKY[4], J. PALMER[3], J. SUN[13], J. WU[1], L. QU[12], Z. WU[6], H. PENG[14], P. OSTEN[3];
[1]Natl. Inst. of Biol. Sciences, Beijing, Beijing, China; [2]Cold Spring Harbor Lab., Northport, NY; [3]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [4]Neurosci., Cold Spring Harbor Lab., Oyster Bay, NY; [5]Neurosci., Weill Cornell Med. Col., New York, Spain; [6]Neurosci., Weill Cornell Med. Col., New York, NY; [7]George Washington Univ., Washington, DC; [8]Boston Univ., Boston, MA; [9]Southeast Univ., Nanjing, China; [10]Cornell University: Weill Cornell Med. Col., New York, NY; [11]Sch. of Electronics and Information Engin., [12]Anhui Univ., Hefei, China; [13]The Univ. of Calgary, Calgary, AB, Canada; [14]Fudan Univ., Shanghai, China

Abstract: SfN Neuroscience 2026 — Control # 2026-S-7301-SfN Theme: J.03.b — Light and electron microscopy | Preference: Nanosymposium PreferredCharacter count (with spaces): 2014 / 2300

Confocal Airy beam oblique light-sheet tomography for brain-wide cell type distribution and neuronal morphology

Abstract body (paste into submission site): Brain-wide cellular architecture and long-range connectivity require volumetric imaging with high throughput, resolution, and signal-to-noise ratio (SNR). Existing light-sheet and point-scanning methods remain limited by trade-offs among field of view, axial resolution, imaging depth, and speed. We developed confocal Airy beam oblique light-sheet tomography (CAB-OLST), an automated single-photon platform combining a scanned nondiffracting Airy beam, rolling-shutter virtual-slit confocal detection, inverted selective plane illumination microscopy geometry, and integrated mechanical sectioning. A spatial light modulator generates a straightened Airy beam with >10-fold extended depth of field relative to a Gaussian beam, and chromatic dispersion compensation supports dual-channel whole-brain imaging.CAB-OLST was validated in cleared adult mouse brains, including Thy1-GFP, tyrosine hydroxylase reporter, Gad2-H2B-GFP, and PV-H2B-GFP lines. The system achieved 0.77 x 0.49 x 2.61 um optical resolution. Compared with standard Airy light-sheet imaging, confocal Airy detection increased neurite contrast 4.7-fold and soma contrast 1.2-fold (n=5 locations; paired t-test; P=0.0021 and P=0.0095). Mechanical sectioning (300 um per cycle) preserved fine-neurite contrast throughout the brain (P=0.0010) and enabled visualization of dendritic spines and axonal boutons. CAB-OLST mapped brain-wide Gad2+ inhibitory neuron distributions at 0.37 x 0.37 x 1.77 um3 voxels in 10 h and reconstructed single-neuron projectomes at 0.26 x 0.26 x 1.06 um3 voxels in 58 h using sparse AAV labeling and Vaa3D tracing. Atlas-registered 3D U-Net segmentation achieved precision 0.969, recall 0.985, and F-score 0.976 (n=3 brains). Dual-channel imaging confirmed reporter and endogenous parvalbumin colocalization.CAB-OLST provides a scalable platform for high-precision whole-brain cell atlasing and single-neuron projectome reconstruction, advancing anatomical neuroscience with accessible single-photon instrumentation.

Keywords: Light sheet fluorescence microscopy (LSFM) | Neuroanatomy | Neuroimaging

Disclosures: X. Qi: None. **R. Muñoz Castañeda:** None. **Y. Yue:** None. **S. Xiao:** None. **L. Ding:** None. **A. Narasimhan:** None. **W. Wang:** None. **Y. Li:** None. **C. Elowsky:** None. **J. Palmer:** None. **J. Sun:** None. **J. Wu:** None. **L. Qu:** None. **Z. Wu:** None. **H. Peng:** None. **P. Osten:** A. Employment/Salary (full or part-time):; Theracast. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Theracast.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

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Program #/Poster #: PSTR114.18/JJ18

Topic: J.03. Anatomical Methods

Support: Brain Science and Brain-like Intelligence Technology – National Science and Technology Major Project 2022ZD0211903
National Science and Technology Innovation 2030 Major Program 2021ZD0202205

Title: Function-Structure Coupled Imaging Enables Brain-Wide Circuit Mapping at Single-Cell Resolution in Freely Behaving Mice

Authors: *W. YE[1,2,3];
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Abstract: Understanding how the activity of individual neurons relates to brain-wide circuit organization during natural behavior remains a fundamental challenge in systems neuroscience. Recent advances in mesoscale imaging have enabled whole-brain structural reconstruction at single-cell resolution; however, functional imaging and structural mapping are typically performed independently, limiting the ability to directly link neuronal dynamics to large-scale circuit architecture. Establishing a unified framework that integrates functional and structural information at single-cell resolution in freely behaving animals remains an important technical challenge.Here, we present a multimodal imaging framework that combines miniaturized two-photon fluorescence imaging in freely behaving mice with single-cell-resolution whole-brain mesoscale fluorescence imaging. To bridge neuronal activity and structural identity, we developed a function-structure coupled dual-color reporter that simultaneously provides activity-dependent functional signals and stable structural labeling within the same cells. Together with whole-brain three-dimensional cellular registration and circuit-tracing approaches, this framework enables the identification of functionally active neurons and their mapping to brain-wide projection patterns.Using this approach, neuronal activity recorded during natural behaviors was linked to corresponding cellular identities and whole-brain structural datasets at single-cell resolution. Functionally defined neurons could be registered across imaging modalities and traced within distributed neural networks, enabling cross-scale integration from local neuronal dynamics to brain-wide circuit architecture. The framework further supports longitudinal tracking of identified neurons and provides a unified platform for structure-function integrated circuit analysis.These results establish a methodological foundation for brain-wide functional circuit mapping at single-cell resolution and provide new opportunities for investigating the neural mechanisms underlying behavior. More broadly, this approach may facilitate the development of next-generation brain mapping technologies and inform future applications in neuroengineering and brain-computer interfaces.

Disclosures: W. Ye: None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.19/JJ19

Topic: J.03. Anatomical Methods

Support: PAPIITIN221326

Title: A Three-Dimensional Interactive Brain Atlas as a Neuroanatomical Framework for Mapping the Muscle-to-PVN Circuit in Response to Exercise

Authors: F. LÓPEZ, *E. L. JAIMES;
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Abstract: The paraventricular nucleus (PVN) of the hypothalamus integrates neuroendocrine and autonomic response signals to maintain metabolic homeostasis. Its heterogeneous neuronal populations (i.e. TRH, CRH and oxytocin) distributed across parvocellular, magnocellular, and descending subregions, are organized along an anterior-to-posterior rostrocaudal axis, making spatial interpretation of circuit tracing data complex. To support the reconstruction of the multisynaptic descending pathway linking PVN neurons to skeletal muscle in the context of voluntary wheel running in future studies, we developed a three-dimensional rat brain model and an interactive digital atlas of the PVN, referenced to *The Rat Brain in Stereotaxic Coordinates* (Paxinos & Watson, 7th edition, 2018). The 3D model was generated in Blender 4.5 from a dissected adult male Wistar-Han rat brain, integrating surface morphology, coloration, and vascularization, generating a 360° rotation animation for multi-angle structural recognition. The interactive digital atlas was developed using standard web technologies (HTML, CSS, SVG, and JavaScript) in the Visual Studio Code editor. The PVN subregions were represented using vector graphic elements located according to the coordinates of the referenced atlas: anterior (-0.60 mm to -1.32 mm from bregma), middle (-1.44 mm to -1.92 mm), and posterior (-2.04 mm to -2.16 mm) PVN subdivisions were built. The interactive digital atlas presents clickable buttons superimposed on each subregion, displaying information about its function, cell type, and distance from the bregma. This coordinate-anchored framework will serve as the spatial reference for assigning immunofluorescence sections to specific PVN subdivisions, enabling subregion-resolved quantification of TRH-immunoreactive neurons across the rostrocaudal axis in sedentary and voluntarily exercised animals of both sexes. The development of these digital resources allows the user to interactively explore the anatomical and functional composition of the brain. These resources will further serve as a spatial scaffold for integrating multisynaptic viral tracing data in future studies, enabling topographic mapping of exercise-dependent neuroplasticity within identified PVN subpopulations. Beyond this project, the atlas provides a freely navigable anatomical platform for cross-laboratory comparison of hypothalamic circuit data and for teaching in neuroendocrine and neuroanatomical science.

Disclosures: F. López: None. **E.L. Jaimes:** None.

Poster

PSTR114: Light and Electron Microscopy

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR114.20/JJ20

Topic: J.03. Anatomical Methods

Title: Cortical Synaptic Organization and Human Intelligence

Authors: *L. BLAZQUEZ-LLORCA[1,2], S. PLAZA-ALONSO[5,3], L. MORALES DE PAZ[5,3], N. CANO-ASTORGA[6,3], A. MERCHAN-PEREZ[1,4], J. DEFELIPE[5,3];
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Abstract: While the biological basis of intelligence has beenextensively studied using histology, neuroimaging, genetics, andtranscriptomics, the relationship between intelligence and the number ofcortical synapses remains largely unexplored. In this study, we applied Focused Ion Beam/Scanning ElectronMicroscopy (FIB/SEM) to analyze the synaptic organization of the middletemporal gyrus (T2; Brodmann area 21) using biopsy samples from fourindividuals undergoing surgery for temporal lobe epilepsy. The analyzed tissuecorresponded to regions with normal EEG activity, resected to provide surgicalaccess to the epileptic focus. All individuals were male, ranged in age from 24to 49 years, and were seizure-free after surgery. Their Full-Scale IntelligenceQuotient (IQ) scores fell within the high-average (115), average (102),borderline (75), and extremely low (68) ranges. Three FIB/SEM stacks of T2layer III, containing ~240-370images each, were analyzed per individual using EspINA software. Approximately 4,000 synapses were analyzed. For eachsynapse, we assessed synaptic density, synaptic size, and postsynaptic target.Preliminary results showed that the high-average-IQ individual had a highersynaptic density, smaller asymmetric synapses (AS), and a greater proportion ofAS established on dendritic spines than the other three individuals. Inaddition, one stack from this individual contained a localized microdomain witha synaptic density of approximately 1.2 synapses/µm³, exceeding the rangepreviously observed by our group across human cortical samples and regions(0.23-0.90 synapses/µm³).Thesefindings reveal substantial local and interindividual variability in thesynaptic organization of the human temporal cortex and suggest a potentialultrastructural profile associated with higher IQ. Further analyses acrosslarger cohorts, additional brain regions, and different cortical layers arerequired to confirm the reproducibility and generalizability of theseobservations.

Disclosures: L. Blazquez-llorca: None. **S. Plaza-Alonso:** None. **L. Morales de Paz:** None. **N. Cano-Astorga:** None. **A. Merchan-Perez:** None. **J. DeFelipe:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.01/JJ21

Topic: J.04. Physiological Methods

Title: An acceleration module for large scale two-photon voltage and calcium imaging

Authors: ***S. TUCKER**[1], T. REIZIS[1], E. GURALNIK[1], D. THEAGENE[1], K. S. GUILLORY[2], S. SHOHAM[1];
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Abstract: Two-photon microscopy enables optical recording from neural populations deep in scattering tissue. Recent major advances in genetically encoded indicators for membrane voltage and neurotransmitters afford new access to rapid dynamics including subthreshold circuit interactions, bursting spike activity, and glutamate release events. However, recording these signals across large fields of view is impossible with conventional resonant-galvanometer two-photon microscopes, which are limited to tens of frames per second. In order to accelerate these systems, we introduce an add-on module that does not replace the core scan engine. Our technique, termed optical-jitter accelerated multiphoton imaging (OJAMI), uses an auxiliary deflector to scan at MHz rates perpendicular to the resonant galvanometer. By reducing the number of mechanically scanned lines and filling the intervening space with extremely rapid inertia-free trajectories, OJAMI increases resonant-galvo frame rates by more than an order of magnitude while preserving field of view and subcellular spatial detail. Using a 16× objective with 0.5 effective NA, it enables the imaging of up to 300 × 700 μm fields of view at 440 Hz. The transmissive module can be installed externally and conjugated to existing scanner optics, which we demonstrate by integrating the module with two distinct microscope platforms. We validated the system in awake mice using calcium and voltage imaging in cortical and olfactory populations. OJAMI resolves rapid calcium-onset dynamics, supports volumetric imaging when combined with axial scanning, and enables recordings from populations of GEVI-expressing neurons, revealing stimulus-evoked spiking and subthreshold responses across extended fields of view. In summary, we introduce a compact, low-cost, and flexible route to high-speed two-photon imaging with otherwise conventional microscopes, lowering the barrier to volumetric calcium imaging and population voltage imaging in vivo.

Disclosures: S. Tucker: None. **T. Reizis:** None. **E. Guralnik:** None. **D. Theagene:** None. **K.S. Guillory:** None. **S. Shoham:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.02/JJ22

Topic: J.04. Physiological Methods

Support: NIH Grant EB027706
ABTA Discovery Grant DG2500080
NIH P30CA043703

Title: A Deterministically Synchronized Widefield Imaging and Virtual Reality Platform for Multimodal Brain Behavior Recording

Authors: *M. YILDIRIM;
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Abstract: Objective Simultaneous recording of brain activity, behaviour, and virtual environments is essential for understanding large-scale neural dynamics during behaviour. However, existing systems often rely on software-based synchronization or post hoc alignment, introducing latency, jitter, and drift that obscure fast brain-behavior interactions.Approach Here, we present a deterministically synchronized widefield calcium imaging platform that unifies neural imaging, high-speed behavioural monitoring, and closed-loop virtual reality (VR) under a shared hardware-defined clock. This system enables millisecond-precision temporal alignment across modalities, including dual-wavelength hemodynamic correction, pupil and orofacial tracking, locomotion sensing, and VR rendering.Main results The platform achieves stable hardware-level synchronization across neural imaging, behavioural recordings, and VR rendering without reliance on software timestamps. It supports widefield imaging rates up to 100 Hz and integrates seamlessly with both ViRMEn and Blender VR engines, exhibiting a mean locomotion-to-VR update latency of ∼1.5 ms. Multimodal recordings during VR navigation demonstrate robust temporal alignment between cortical activity, facial dynamics, pupil signals, and locomotion.Significance This system provides a deterministic multimodal framework for studying brain-behaviour relationships during active behaviour. By enabling millisecond-precision synchronization across neural imaging, behaviour, and virtual environments, this platform enables causal investigation of brain-behaviour interactions at millisecond precision and provides a foundation for next-generation closed-loop neuroengineering experiments.

Disclosures: M. Yildirim: None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

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Program #/Poster #: PSTR115.03/JJ23

Topic: J.04. Physiological Methods

Support: CZI Grant 1384/21
ISF Grant 1385/21
ERC Grant 101040128

Title: In vivo imaging of autophagy dynamics in the living mouse brain

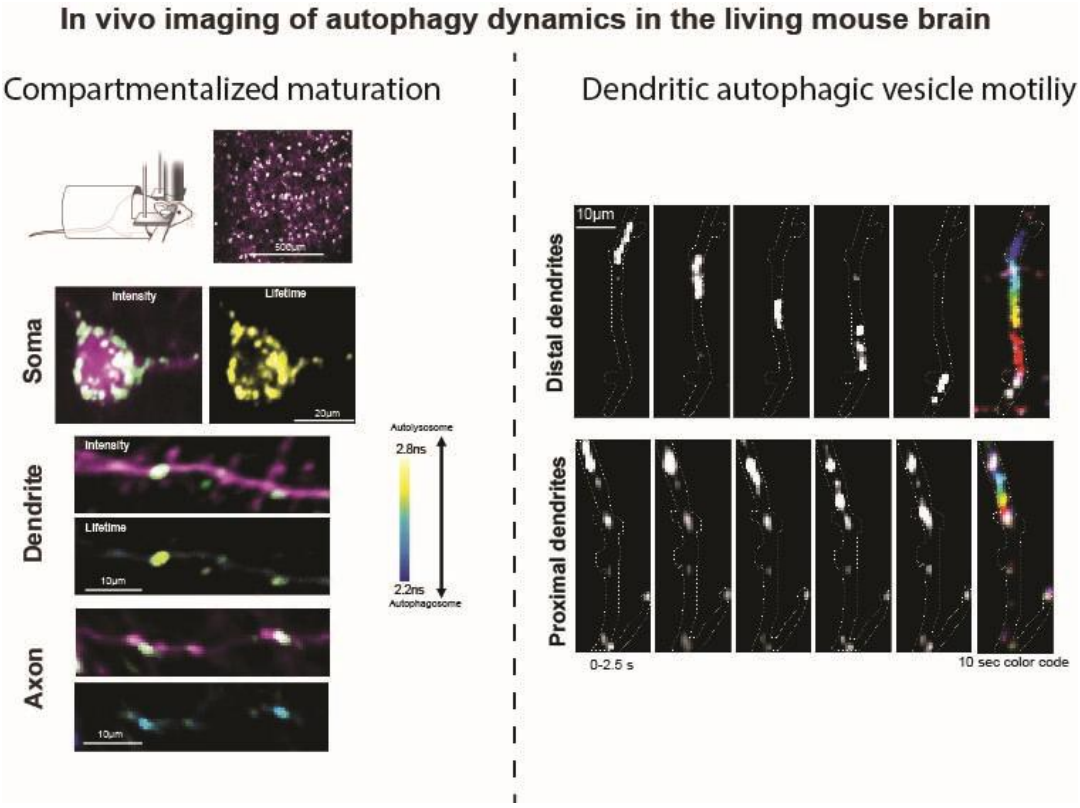
Authors: *M. A. MAMAN[1], T. LAVIV[2];
[1]Dept. of Neurosci. and Brain Disorders, [2]Physiol. and Pharmacol., Tel Aviv Univ., Tel Aviv, Israel

Abstract: Autophagy, a lysosomal degradation pathway, is fundamental for regulating neuronal development, plasticity, and local metabolism. However, the dynamics and compartment-specific regulation of neuronal autophagy in the intact mammalian brain remain poorly understood.

Here, we developed a pH-sensitive, fluorescence-based autophagy biosensor that enables in vivo imaging of autophagy dynamics in the living mouse brain. Using CRISPR/Cas9-mediated manipulation of key autophagy genes, we validated the sensitivity and specificity of this approach. Additionally, we performed CLEM to correlate the fluorescent sensor with autophagosomes and autolysosomes in EM images.

Importantly, we found that autophagic vesicle motility is differentially regulated across dendritic compartments of layer 2/3 cortical neurons, with significantly higher vesicle mobility in distal dendrites compared to proximal dendrites. Furthermore, long-term sensory deprivation induced distinct changes in autophagic vesicle dynamics, demonstrating that neuronal experience modulates autophagy in vivo.

In addition, we observed marked differences in basal autophagy levels among major brain cell types, including excitatory and inhibitory neurons, astrocytes, and oligodendrocytes, supporting cell-type-specific roles for autophagy in the intact brain. This approach enables investigation of autophagy under physiological, behavioral, and disease-related conditions. It provides a powerful platform for studying the role of autophagy in neural plasticity, brain function, and neurological disease.



Disclosures: M.A. Maman: None. **T. Laviv:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.04/JJ24

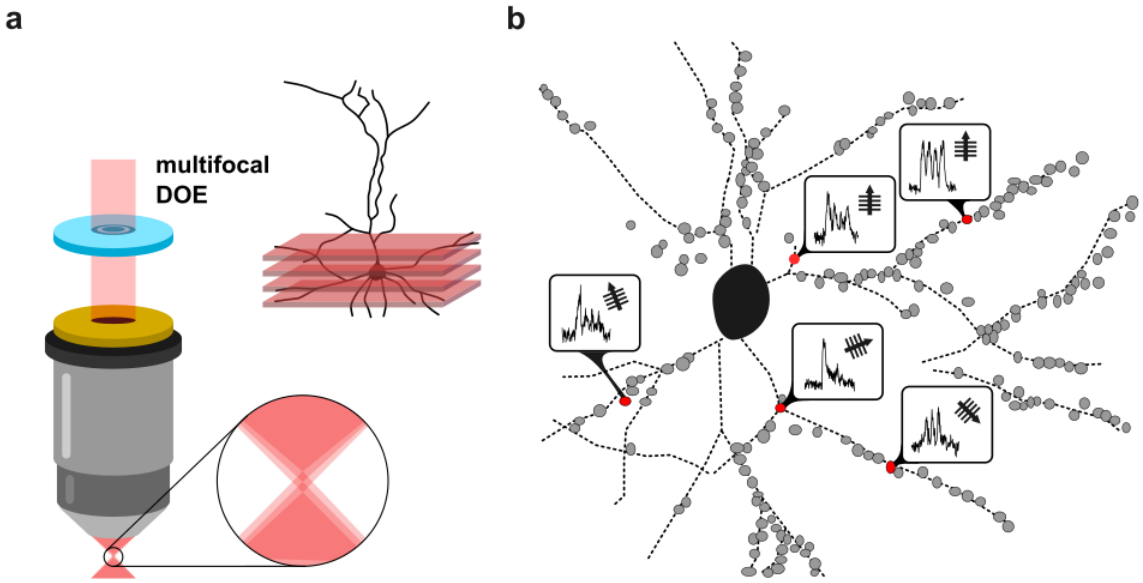
Topic: J.04. Physiological Methods

Support: Hertie Foundation
Synergy - Munich Cluster for Systems Neurology

Title: High-speed volumetric synapse mapping in vivo using multifocal diffractive optical elements

Authors: *J. RICHTER, Y. ZHANG, Y. CHEN, A. KONNERTH;
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Abstract: The monitoring of single-synapse activity in vivo primarily relies on two-photon calcium or glutamate imaging. However, these methods are limited to the visualization of single confined focal planes. This severely limits the number of inputs that can be observed simultaneously. New imaging methods, particularly those using Bessel-droplet excitation (Wei Chen ⋯ & Na Ji, Nature Methods, 2024), have decisively advanced volumetric in vivo imaging. However, their frame rates are limited, and the implementation is relatively tedious. High frame rate recordings are particularly useful for the volumetric imaging of fast single-synapse glutamate signals. Here, we introduce a simple volumetric imaging method using drop-in multifocal diffractive optical elements (DOEs). For the mapping of single sensory inputs, we used volumes of 200x200X35 µm at 40 Hz or 50x150x35 µm at 200 Hz. The example in Fig. 1 illustrates mapping of visual stimulation-activated inputs onto a layer 2/3 neuron in the mouse visual cortex expressing the 'slow' iGluSnFR4 (Abhi Aggarwal ⋯& Kaspar Podgorski 2026). In this experiment, we determined the activity of more than 200 active spines at 40 Hz with a df/f of up to 400%, while simultaneously recording the neuron's output signal by recording from the axon bouton. We estimate that mapping with the 'fast' iGluSnFR4 (Abhi Aggarwal ⋯& Kaspar Podgorski 2026) enables simultaneous monitoring of up to 50 spines at 200Hz. Finally, our method is easily compatible with multi-color recordings, allowing, for example, combined glutamate and calcium imaging experiments. In conclusion, volumetric imaging using DOEs can be readily implemented in any commercial two-photon microscope and allows effective high-speed recordings with good signal-to-noise ratios.



Disclosures: J. Richter: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Applicant. **Y. Zhang:** None. **Y. Chen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Applicant. **A. Konnerth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Applicant.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

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Program #/Poster #: PSTR115.05/KK1

Topic: J.04. Physiological Methods

Support: NIH NIBIB R01EB037653

Title: Fast Two-photon Microscopy by Neuroimaging with Oblong Random Acquisition (NORA)

Authors: *E. WHANG, B. J. ZHU, S. THOMAS, J. YI, A. S. CHARLES;
Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Advances in neural imaging have enabled neuroscientists to study how large neural populations conspire to produce perception, behavior and cognition. Despite many advances in optical methods, there exists a fundamental tradeoff between imaging speed, field of view, and resolution that limits the scope of neural imaging, especially for the raster-scanning multi-photon

imaging needed to image deeper into the brain. One approach to overcoming this trade-off is computational imaging: the co-development of optics designed to encode the target images into fewer measurements that are faster to acquire, with algorithms that compensate by inverting the optical coding to recover a larger or higher resolution image. We present here one such approach for raster-scanning two-photon imaging: Neuroimaging with Oblong Random Acquisition (NORA). NORA quickly acquires each frame in a microscopy video by subsampling only a fraction of the fast scanning lines, ignoring large portions of each frame. NORA mitigates the loss of information by 1) extending the point-spread function in the slow-scan direction to effectively integrate the fluorescence of several lines into a single set of measurements and 2) imaging different, randomly selected, lines at each frame. Rather than reconstruct the video frame-by-frame, NORA recovers full video sequences via nuclear-norm minimization on the pixels-by-time matrix, for which we prove theoretical guarantees on recovery. We simulated NORA imaging using the Neural Anatomy and Optical Microscopy (NAOMi) biophysical simulator, and used the simulations to demonstrate that NORA can accurately recover 400 um X 400 um fields of view at subsampling rates up to 20X, despite realistic noise and motion conditions. As NORA requires minimal changes to current microscopy systems, our results indicate that NORA can provide a promising avenue towards fast imaging of neural circuits.

Disclosures: E. Whang: None. **B.J. Zhu:** None. **S. Thomas:** None. **J. Yi:** None. **A.S. Charles:** None.

Poster

PSTR115: Optical Methods I

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Program #/Poster #: PSTR115.06/KK2

Topic: J.04. Physiological Methods

Support: RS-2024-00402116
RS-2024-00335546

Title: Dual-color miniaturized fluorescence microscope for real-time neural imaging in the rodent brain

Authors: *H. JEONG[1], Y. CHO[4], S. JUN[1,2,3];
[1]Dept. of Electronic and Electrical Engin., [2]Div. of Brain and Cognitive Sci., [3]Ewha Brain Inst., Ewha Womans Univ., Seoul, Korea, Republic of; [4]Dept. of Med. and Mol. Genet., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: A precise understanding of neural circuit function requires methodologies capable of monitoring neuronal activity with single-cell resolution. Optical neural recording using genetically encoded calcium indicators (e.g., GCaMP) has emerged as a powerful approach for monitoring neuronal population dynamics *in vivo* with real-time, single-cell resolution. Miniaturized fluorescence microscopes (miniscopes) have been widely adopted for large-scale

imaging of neuronal activity in freely behaving animals, as their head-mounted design enables simultaneous neural recording during diverse behavioral tasks. Dual-color fluorescence imaging further extends the capabilities of miniscope-based recordings by enabling the simultaneous monitoring of distinct neuronal populations within the same field of view, thereby providing additional functional information beyond that obtainable with single-wavelength imaging. However, conventional dual-color imaging approaches typically rely on time-division multiplexing of excitation sources, which reduces temporal resolution, while chromatic aberration remains a persistent challenge. In this study, a color CMOS image sensor was utilized to directly separate wavelength-dependent fluorescence signals, enabling channel registration despite chromatic aberration without the need for sequential image acquisition. Furthermore, wavelength-dependent focal shifts within the optical system were leveraged to extract limited depth information from the recorded fluorescence signals. The optical and mechanical design was developed based on the UCLA miniscope platform, thereby maintaining compatibility with the existing data acquisition (DAQ) framework while extending its functionality for dual-color imaging applications. This approach provides a practical and scalable solution for multicolor neural imaging in freely behaving animals.

Disclosures: H. Jeong: None. **Y. Cho:** None. **S. Jun:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

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Program #/Poster #: PSTR115.07/KK3

Topic: J.04. Physiological Methods

Support: NIH Grant R15NS135507

Title: Commutator-assisted fiber bundle imaging system for neural and behavioral recording in freely behaving animals

Authors: D. SHEN, L. ZHAO, ***B. LIANG**;
Univ. of North Dakota, Grand Forks, ND

Abstract: Exploration of neural mechanisms underlying complex behaviors in neuroscience experiments requires the recording and/or modulation of neural activity in naturalistic contexts. Miniaturized optical imaging systems and genetically encoded indicators have become widely used tools for studying brain circuit dynamics during naturalistic behaviors in various animal models. Besides wide-field miniature microscopes and single optical fiber-based systems, fiber bundle-based imaging systems, utilizing either single-photon or two-photon light sources, have also been developed to optically record or modulate the activity of neurons and glial cells in freely behaving mice. They enable structured illumination for single cell optogenetic modulation while limited in freely behaving animals due to tether twisting caused by restricted rotation. Custom commutators and electrical-tether-based solutions either complicate image processing or

are incompatible with fiber bundles. We describe a compact fiber bundle imaging system that dynamically adjusts the position of the entire optical assembly in response to the animal's movements. It incorporates torque sensing with IMU sensors at the proximal end of the fiber bundle, coupled with a motorized rotary stage to rotate the optical system accordingly. A slip ring is used to provide power and enable rotation, while imaging data are managed by an onboard microcomputer integrated with the optical assembly. Our system also supports multichannel imaging in combination with genetically encoded sensors that have distinct spectral profiles. This system complements existing miniaturized optical imaging tools and offers a new paradigm for experiments requiring imaging and modulation of neural activity in freely behaving animals.

Disclosures: D. shen: None. **L. Zhao:** None. **B. Liang:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.08/KK4

Topic: J.04. Physiological Methods

Title: Coding architectures for drive and action drift independently across the same neuronal population

Authors: *L. ENCARNACION-RIVERA[1], E. RICHMAN[3], L. LUO[2], K. DEISSEROTH[2]; [1]Stanford Univ., PALO ALTO, CA; [2]Stanford Univ., Stanford, CA; [3]Neurosci., Stanford, Palo Alto, CA

Abstract: Motivational drives (such as thirst and hunger) link physiological needs to actions favoring survival. A critical challenge encountered by living organisms is that all drives are conflicting, since typically only a single need can be addressed by action at one moment in time. To explore how neural dynamics may underlie unitary action in the presence of multiple distinct survival needs, we measured neural activity across the brain (5 animals, 1,623 neurons, 32 brain regions) with single-cell and single-spike resolution during unstructured foraging for food and water in the setting of hunger and thirst drives. We first observed, for most individual neurons that had been found to show selectivity for either hunger or thirst drive (23.2% of all recorded neurons), that cellular spiking activity represented not only that specific drive but also less-specific foraging actions (96% overlap). However, at the neuronal population level, we observed drive and action information to be represented along largely independent dimensions in brain-wide state space (>0.9 AUC). In exploring this distinction, we identified differential neural activity patterns propagating along brain-spanning dimensions discrete different choices and actions- revealing the global fast-timescale dynamics underlying food- and water-seeking drive states, the transitions between these drive states, and the quiescent intervals between bouts of foraging. We employed the natural perturbation provided by representational drift to determine if drive and action representations could shift independently within the same distributed brain-wide

populations of neurons; surprisingly, when we quantified the activity of identified neurons over chronic (multi-day) timescales, we found that drive representations drifted more rapidly than those of actions across the same neurons ($R^2 = 0.30$ for drive versus $R^2 = 0.74$ for actions). Together, these measurements of acute and chronic brain-wide dynamics during free behavior revealed a distinctive population-coding architecture underlying natural survival drives, which enables reliable execution of action while accommodating variable drive states separably superimposed on the same neurons.

Disclosures: L. Encarnacion-Rivera: None. **E. Richman:** None. **L. Luo:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.09/KK5

Topic: J.04. Physiological Methods

Title: Deep brain mesoscale calcium imaging in freely behaving mice

Authors: *I. OLADEPO[1], D. FLINK[2], K. SAXENA[3], A. HAMID[4], S. B. KODANDARAMAIAH[5];
[1]Mechanical Engin., Univ. of Minnesota, Twin Cities, Saint Paul, MN; [3]Mechanical Engin., [4]Dept. of Neurosci., [2]Univ. of Minnesota, Minneapolis, MN; [5]MECHANICAL ENGINEERING, Univ. Of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Widefield imaging of dopamine dynamics in the dorsal striatum has revealed spatially organized, wave-like activity patterns implicated in reward-based learning and spatiotemporal credit assignment. However, these findings have been limited to head-fixed preparations, leaving the relationship between striatal dopamine waves and naturalistic behavior largely unexplored. Although head-mounted miniscopes have been used to image the dorsal striatum in freely behaving animals, they typically rely on GRIN lens relay optics. These implants are highly invasive and constrain the field of view to single-cell-scale coverage, which is insufficient for capturing mesoscale dynamics. Here, we introduce a miniaturized, head-mounted fluorescence microscope designed for long working distance, widefield calcium imaging of the dorsal striatum in unrestrained mice. The 4.75 g device achieves a 13.45 mm working distance, 13.92 μm center resolution, and a 16.8 mm² field of view, enabling optical access to the deep brain structure without invasive relay optics. Its design supports quick docking and undocking and enables extended recording sessions during unrestrained behavior. To characterize striatal population dynamics during naturalistic behavior, we imaged freely moving mice during a cued open-field reward task and a social interaction paradigm with naive mice. These widefield calcium recordings demonstrate that deep-brain mesoscale striatal dynamics are accessible in freely behaving animals during both reward-based and social behaviors.

Disclosures: I. Oladepo: None. **D. Flink:** None. **K. Saxena:** None. **A. Hamid:** None. **S.B. Kodandaramaiah:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.10/KK6

Topic: J.04. Physiological Methods

Title: Validation of a Single- and Dual-Color Fluorescence Lifetime Fiber Photometry Platform for Simultaneous In Vivo Measurement of Calcium and Dopamine

Authors: *E. BÉLANGER[1], A. TABAK[2], E. KARAMEHMEDOVIC[2], É. DROUIN[1], Q. LEJEUNE[1], Y. ALIKACEM[1], K. BAKHSHETYAN[1], A. LAVOIE[1], H. DEHEZ[1];
[1]Doric Lenses, Québec, QC, Canada; [2]Doric Lenses, Sarajevo, Bosnia and Herzegovina

Abstract: Validation of a Single- and Dual-Color Fluorescence Lifetime Fiber Photometry Platform for Simultaneous In Vivo Measurement of Calcium and Dopamine
Introduction: Fiber photometry (FP) enables real-time monitoring of neuronal activity using fluorescent biosensors like calcium and dopamine. Combined with multi-animal multiplexing, it provides efficient access to reward and learning and is widely used to study the interplay between excitability and neuromodulation in freely behaving animals.
Fluorescence lifetime (FLi) offers a robust, quantitative readout independent of signal intensity and resistant to artifacts such as motion, photobleaching, and expression variability. It enables precise detection of biosensor conformational changes and is well suited for monitoring changes in neural and biochemical activity.
Rationale: Until recently, no commercially available FLiP (fluorescence lifetime-based fiber photometry) systems supported dual-channel architectures for parallel two-animal multiplexing, limiting throughput. This gap also extends to dual-color measurements of calcium and dopamine in vivo, restricting broader adoption. Such capabilities would enable dissociation of neuronal and dopaminergic signals while improving efficiency, providing a key advantage for studying freely behaving animals.
Results: We developed and validated a versatile single- and dual-color FLiP platform supporting measurements in animals, parallel multiplexing across two animals, and simultaneous dual-biosensor interrogation within a single animal. The system is based on a pulse-sampling architecture combining two picosecond pulsed lasers (400 kHz; 450, 488, 515, or 660 nm) for excitation, nanosecond-scale photodetectors for fluorescence detection, and high-frequency digitization (up to 6.4 GHz) to capture emitted signal profiles. This enables real-time mono-exponential fitting and fluorescence lifetime extraction at rates up to 25 Hz. One configuration is optimized for the calcium Tq-Ca-FLITS and dopamine FLIM-DA1.0 biosensors. Metrological validation using solid lifetime standards demonstrated picosecond-scale accuracy, high precision, minimal drift, and strong inter-session reproducibility across all single-color modes. In dual-color operation, the system achieved robust spectral separation with negligible crosstalk,

enabling reliable multiplexed measurements.
Conclusion: Now commercialized as the Doric FluoPulse™ system, this dual-channel FLiP platform establishes a robust technological foundation for improved throughput and simultaneous in vivo monitoring of neuronal activity and dopaminergic signaling.

Disclosures: E. Bélanger: A. Employment/Salary (full or part-time):; Doric Lenses. **A. Tabak:** A. Employment/Salary (full or part-time):; Doric Lenses. **E. Karamehmedovic:** A. Employment/Salary (full or part-time):; Doric Lenses. **É. Drouin:** A. Employment/Salary (full or part-time):; Doric Lenses. **Q. Lejeune:** A. Employment/Salary (full or part-time):; Doric Lenses. **Y. Alikacem:** A. Employment/Salary (full or part-time):; Doric Lenses. **K. Bakhshetyan:** A. Employment/Salary (full or part-time):; Doric Lenses. **A. Lavoie:** A. Employment/Salary (full or part-time):; Doric Lenses. **H. Dehez:** A. Employment/Salary (full or part-time):; Doric Lenses.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.11/KK7

Topic: J.04. Physiological Methods

Support: NIH Grant R01NS118289
NIH Grant R21EB035306
NSF CAREER 1847141
Burroughs Wellcome Fund 1015761

Title: Temporally Focused Elliptical Beam Miniaturized Two-Photon Microscopy for Volumetric Imaging in Freely-Moving Mice

Authors: *B. MATTISON, Z. ZHANG, S.-J. LIU, N. SPURR, F. TIAN, W. YANG;
Univ. of California Davis, Davis, CA

Abstract: Miniaturized two-photon microscopes are powerful tools to record neural activity at cellular resolution in freely-moving animals. The point-by-point sampling nature of two-photon limits imaging frame rate when sampling from large volumes because in addition to scanning a large single plane field-of-view (FOV), refocusing to additional planes puts further strain on the available frame rate. Here, we report a two-photon miniaturized microscope which uses a temporally focused elliptical beam that can image volumetric neuronal activity at cellular resolution with a high speed in freely-moving mice. Rather than illuminating the sample with a diffraction-limited spot, we shape the beam into an elliptical spot with 8 μm lateral full width half-maximum (FWHM) in the long axis to match the size of neuronal cell bodies. To reduce the axial tail of the point spread function (PSF), we introduce a temporal focusing scheme by inserting a grating into the beam path. We incorporate an electrically tunable lens (TLens) for volumetric plane refocusing during imaging. Using our miniaturized microscope, we performed fast volumetric calcium imaging in mouse secondary motor cortex (M2) transfected with

GCaMP calcium indicators over a cortical volume of 500 μm × 500 μm × 300 μm. We find that increasing the density of axial plane sampling from 5 planes at 75 μm spacing to 16 planes at 20 μm increases the number of non-repeated neurons extracted by over 2-fold. Due to the reduced number of scanning rows per plane, the elliptical beam sampling maintains an 11 Hz volumetric stack rate at 16 planes. Further, the temporal focusing strategy greatly decreases the percentage of repeated neurons across planes. Volumetric recordings enabled identification of neural populations in M2 tuned to different behavioral conditions such as movement, climbing, and grooming. Our beam shaping miniaturized two-photon microscope enables recording neural activity from dense cortical volumes in freely-moving mice and will be important to study large-scale neuronal circuits during natural mouse behaviors.

Disclosures: B. Mattison: None. **Z. Zhang:** None. **S. Liu:** None. **N. Spurr:** None. **F. Tian:** None. **W. Yang:** None.

Poster

PSTR115: Optical Methods I

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Topic: J.04. Physiological Methods

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Minnesota Robotics Institute (MnRI)
MnDRIVE RSAM
The McKnight Foundation
UMN Mechanical Engineering Department
UMN Interdisciplinary Doctoral Fellowship

Title: Robotic-2p: a robotically actuated microscope for advanced two-photon imaging in freely locomoting mice

Authors: *S. PAN[1], P.-H. CHENG[1], T. BECKERLE[1], D. FARINELLA[2], J. HOPE[1], R. AL KHOURY[2], J. GABLE[2], H. JAYAKUMAR[2], Z. VIAVATTINE[1], K. SAXENA[1], T. KOWALEWSKI[1], A. KERLIN[2], S. B. KODANDARAMAIAH[1,3];
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Abstract: Computations in the brain involve dynamics across many anatomical and spatial scales - from integration at individual synapses to brain-wide neuromodulatory shifts. Studying these computations under naturalistic conditions is critical to ensure that the networks under study are operating in dynamical regimes shaped by evolution, rather than perturbed regimes caused by restrictive experimental setups. High-resolution imaging technologies, such as multiphoton imaging, have revolutionized systems neuroscience by allowing simultaneous

recording and manipulation of brain activity at different scales. However, traditional microscopy techniques require unnatural head fixation, limiting the study of natural motor, self-motion, and sensory-spatial interactions. Miniaturized imaging devices have been developed to address this limitation, but these compromise performance and are incompatible with many advanced 2P imaging techniques.
We have developed Robotic-2P, a robotically actuated two-photon microscope that moves with the animal and enables imaging of neural activity during complex, freely moving behaviors. The system features a closed-loop admittance controller that detects mN-scale forces applied by the mouse through a 6-DOF force sensor. It drives a gantry in the x, y, and yaw axes, allowing the animal to maneuver heavy imaging headstages with minimal effort. We demonstrate mice maneuvering robotic imaging headstages weighing up to 15 kg in open field arenas. Quantitative analysis revealed velocity and acceleration distributions comparable to those of freely behaving mice. Imaging of fixed fluorescent samples during robotic actuation demonstrated image quality comparable to stationary conditions, with minimal vibration-induced artifacts during accelerations up to 1 m/s^2. To demonstrate support for structured behavior beyond locomotion, mice performed reward-guided navigation tasks in reconfigurable open-field and figure-8 maze arenas, maintaining natural trajectories. These results establish a foundation for high-performance neural imaging in complex reconfigurable physical spaces. Further, the Robo-2P provides a flexible platform for developing high-performance neural imaging systems for studying freely locomoting behavior, bridging the gap between benchtop imaging systems and freely moving neuroscience experiments.

Disclosures: S. Pan: None. **P. Cheng:** None. **T. Beckerle:** None. **D. Farinella:** None. **J. Hope:** None. **R. Al Khoury:** None. **J. Gable:** None. **H. Jayakumar:** None. **Z. Viavattine:** None. **K. Saxena:** None. **T. Kowalewski:** None. **A. Kerlin:** None. **S.B. Kodandaramaiah:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-founder of Objective Biotechnology Inc..

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.13/KK9

Topic: J.04. Physiological Methods

Title: ROSEBUD: Simultaneous EEG and widefield optical imaging for assessing cortical-behavioral dynamics in freely behaving rodents

Authors: *S. JAMES[1], S. FISCHBACH[2];
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Abstract: ROSEBUD (Recording Optical Signals and EEG for Behavioral Unified Dynamics) is a multimodal platform combining electroencephalography (EEG), widefield optical imaging (WOI), and behavioral analysis to assess cortical-behavioral dynamics in freely behaving

rodents. The relationship between cortical function and behavior is shaped by interacting neural, glial, and vascular processes that dynamically regulate cortical state and may provide important targets for therapeutic development. ROSEBUD was developed as an integrated recording and analysis framework to capture global and regional spatiotemporal cortical correlates of behavior across domains relevant to neurological and neurodevelopmental dysfunction. Animals were prepared with a cranial window for WOI and skull-mounted EEG electrodes. A wireless head-mounted recording device transmitted EEG data over Wi-Fi, while WOI captured mesoscale neural activity using genetically encoded calcium indicators and hemodynamic fluctuations through intrinsic optical signals. Behavioral performance was analyzed using custom MATLAB pipelines designed to align behavioral epochs with EEG spectral features, calcium-related optical dynamics, and hemodynamic responses. Behavioral assessments included open field, object recognition, elevated zero maze, and three-chamber social testing. Preliminary recordings from three animals demonstrated successful alignment of behavioral events with EEG, calcium-related optical signals, and hemodynamic responses across multiple behavioral assays. Across assessments, non-rest behavioral epochs were associated with average increases of 28% in EEG activity, 8% in calcium-related optical fluctuations, and 16% in hemodynamic responses. These findings demonstrate the feasibility of ROSEBUD as an integrated EEG-WOI-behavior platform for mapping cortical state dynamics during freely moving behavior. This approach may improve interpretation of neural and vascular contributions to behavior and provide a framework for identifying cortical signatures relevant to disease mechanisms and therapeutic development.

Disclosures: S. James: None. **S. fischbach:** None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.14/KK10

Topic: J.08. Methods to Modulate Neural Activity

Support: STI2030-Major Projects 2022ZD0212100

Title: Long-working-distance miniature two-photon microscopy enables flexible optical access for deep-brain imaging from mice to nonhuman primates

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Abstract: Unrestrained neural imaging across species, from rodents to nonhuman primates, is essential for understanding circuit mechanisms underlying natural behavior and cognition. However, current miniature two-photon microscopes (m2PMs) are constrained by short working distances (WDs), limited compatibility with deep-brain optical access interfaces, and insufficient adaptability to nonhuman primates. Here, we developed a long-WD m2PM platform centered on interchangeable, two-color achromatic miniature objectives with 2- and 3-mm WDs and

improved tolerance to refractive-index mismatch. This optical design enables flexible integration with brain-access strategies spanning different depth ranges, including cranial coverslips, cannulas, refractive-index-matched, low-obstruction T-shaped glass rods (T-rods), prisms, and GRIN lenses, thereby supporting access from superficial cortex to deep brain structures. In freely moving mice, coupling the long-WD m2PM with a small cannula or T-rod interface enabled high-resolution volumetric imaging over 700 μm from CA1 to DG, with axon-level resolution and a 600 × 500 μm FOV while preserving hippocampal integrity. A fast remote axial-focusing module further allowed simultaneous functional imaging of CA1 and DG neurons during free behavior. In marmosets, an optimized lightweight cable-protection design supported stable calcium imaging of auditory cortical neurons during naturalistic auditory behavior. In head-unrestrained macaques, integration with a miniature XYZ motion stage and high-efficiency fluorescence collection enabled robust neuronal imaging with adjustable FOVs and improved SNR. We further incorporated TPGNet, a cross-species denoising strategy, to enhance the usability of deep-brain and primate imaging data under low-SNR conditions. Together, this long-WD m2PM platform establishes a versatile technical route that combines deep-brain optical access, cross-layer volumetric scanning, species-specific mechanical adaptation, and computational signal recovery. These capabilities expand miniature two-photon imaging from conventional superficial preparations toward flexible, high-resolution structural and functional imaging of deep brain circuits across mice, marmosets, and macaques.

Disclosures: R. Wu: None.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.15/KK11

Topic: J.04. Physiological Methods

Support: Health + Life Science Alliance, ExploreTech! grant
Scientific Software Center Heidelberg Open Call 2025
Medical Faculty Mannheim, Förderprogramm SEED

Title: Neuronal Sequencer: A Cross-Domain Software Framework for Control of Neural Networks

Authors: *A. FORMOZOV[1], S. VINTILA[1,2], Y. ATES[1], C. BAIO[1], B. VON HÜNERBEIN[3], J. GOELTZ[3], H. MACK[4], J. BOWYER[4], D. O. PASTENE[5], L. KEEGAN[4], M. BOTH[2], M. A. PETROVICI[3], S. WIEGERT[1];
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Abstract: Experimental neuroscience, computational neuroscience, and neuromorphic engineering, all consider neural (neuronal) networks as the fundamental substrate for computation. However, the methods used to control and investigate these networks differ drastically across these disciplines. While computational models offer full access to internal dynamics and parameters, and flexible input definition, physical computing substrates are far more difficult to interface with and control. This affects, in particular, analog neuromorphic hardware, especially when it is based on new materials and physical computing paradigms, but by far the greatest challenges appear for biological systems. Recent advances in all-optical and electrophysiological bidirectional interfacing are gradually closing this gap, enabling high-throughput readout and control of biological neuron states. Building on these advances and leveraging architectural and dynamical commonalities between neural networks across disciplines, we propose a universal framework for controlling these networks, regardless of whether they are biological, virtual, or neuromorphic. Precise control of the input to the intelligent systems can be key to understanding their operation, as the input not only streams information of different kinds into the system but also determines its dynamical and computational state. In an experimental setting, flexible input control promotes a practical realization of computation in neurobiological networks and can be recruited for rigorous investigation of their computational properties in experiments with closed-loop adaptive designs. To demonstrate the feasibility of this approach, we have developed the Neuronal Sequencer (NeuroSeq), a software package that allows computational neuroscientists to interact with biological and neuromorphic systems as if they were virtual simulations - and conversely, allows experimentalists to run computational models as if they were real experiments. This framework will bridge historically separate methodological cultures, promoting a seamless exchange of concepts, theories, and empirical findings across fundamental research, practical applications, and education.

Disclosures: A. Formozov: None. **S. Vintila:** None. **Y. Ates:** None. **C. Baio:** None. **B. von Hünerbein:** None. **J. Goeltz:** None. **H. Mack:** None. **J. Bowyer:** None. **D.O. Pastene:** None. **L. Keegan:** None. **M. Both:** None. **M.A. Petrovici:** None. **S. Wiegert:** None.

Poster

PSTR115: Optical Methods I

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Gatsby Charitable Foundation

Knight Initiative for Brain Resilience
Chan Zuckerberg Biohub San Francisco
Stanford Bio-X
HHMI

Title: Intrinsic space-time couplings governing multi-scale cortical dynamics

Authors: *A. WHITE[1], **Y. WANG**[2], J. KOCHALKA[3], A. Y. HAO[4], C. LI[7], S. GANGULI[5], T. CLANDININ[6], M. Z. LIN[8], K. DEISSEROTH[5];
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Abstract: The neocortex covers a vast expanse of the mammalian brain and represents the principal target of clinical neuromodulation; however, the global principles of neocortical operation have been challenging to identify. In this regard, a limitation has been tracking activity with cortex-wide spatial coverage while maintaining access to the millisecond temporal resolution of neuronal firing— a crucial combination not achievable with existing recording technologies. Here we introduce and apply conformal immersion microscopy (CIM), which uses a custom lens and glycerol immersion to image a curved focal plane with a very large numerical aperture (NA of 0.6). In combination with the next generation of voltage indicators, CIM enables activity tracking across the entire dorsal cortex with millisecond temporal resolution and 100 μm spatial resolution (thus spanning five orders of magnitude in time and four in space), at sufficient sensitivity to resolve single-trial activity beyond 100 Hz. Drawing on physics-based frameworks, we apply multiscale analysis to identify a fundamental frequency-dependent coherence length that partitions the neocortex into discrete dynamical elements with well-defined propagation speeds, boundaries, and scale-invariant dynamics (N = 4 mice, n = 25 sessions). Dual-color imaging with voltage (ASAP7y) and Ca2+ indicators (srGECO) reveals this architecture is conserved across sub- and suprathreshold regimes of neural activity (N = 4, n = 25). The dynamical architecture proved robust to specific pharmacological (LSD, N = 3, n = 3), physiological (targeted optogenetic stimulation with rsChRmine, N = 5, n = 9), and genetic (CNTNAP2 knockout, N = 2WT + 2KO, n = 4) interventions. However, exceptionally powerful perturbations — including ketamine (N = 4, n = 4), diazepam (N = 3, n = 3), and strong optogenetic overstimulation (N = 5, n = 9) — could selectively override elemental boundaries or modulate specific elements while preserving global dynamics. Together, these findings enable measurement of intrinsic spatiotemporal parameters governing the dynamical organization of neocortex, which may provide a foundation for mechanistically-informed basic and translational understanding.

Disclosures: A. White: None. **Y. Wang:** None. **J. Kochalka:** None. **A.Y. Hao:** None. **C. Li:** None. **S. Ganguli:** None. **T. Clandinin:** None. **M.Z. Lin:** None. **K. Deisseroth:** Other; K.D. is a co-founder and a scientific advisory board member of Stellaromics and Maplight Therapeutics and advises RedTree and Modulight.bio..

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

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NINDS 1RM1NS132981
Stanford Bio-X Seed Grant

Title: Frequency-resolved directional elements of millisecond-timescale cortical dynamics

Authors: *J. KOCHALKA[1], A. WHITE[2], Y. WANG[3], A. Y. HAO[4], T. R. CLANDININ[5], M. Z. LIN[7], K. DEISSEROTH[6];
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Abstract: Orderly sequential activation of neural circuits appears to be a fundamental principle of brain organization across spatial and temporal scales. At the level of dorsal cortex, spontaneous activity unfolds as structured ensemble sequences mirroring those evoked by sensory stimulation, and recent work has demonstrated that low-dimensional spatiotemporal structure underlies cortex-wide dynamics. However, existing optical approaches for large-scale cortical recording have relied predominantly on genetically encoded calcium indicators, whose slow extrusion kinetics fundamentally limit access to fast neural dynamics. Whether distinct spatiotemporal organization exists at higher frequencies—theta, beta, and gamma—or whether fast dynamics are simply a higher-frequency reflection of the same slow fluctuations has therefore remained unknown.
To address this, we performed cortex-wide spontaneous activity screening in head-fixed, awake mice (N=4) using ASAP7y (a novel high-sensitivity genetically encoded voltage indicator (GEVI) expressed under the control of the CaMKIIα genetic regulatory element), imaged through a cleared-skull preparation with a custom widefield macroscope optimized for photon collection efficiency. Applying an unsupervised convolutional matrix factorization pipeline to band-limited voltage signals, we recovered a compact set of spatiotemporal directional elements—conserved propagating patterns of cortical activity spanning five major functional systems: Anterolateral (AL), Active Sensory (AS), Medial Somatomotor (MS), Visual (V), and

Medial Associative (MA). These elements were recovered across delta, theta, beta, and gamma frequency bands, demonstrating that structured directional cortical dynamics extend through the full range of physiologically relevant timescales. Band-specific differences were observed—higher frequency bands produced stronger source-region loadings for AS, MS, and V, while gamma showed a sink bias in AL—but the core organizational motifs were preserved across all bands. Pairwise cross-correlations among matched elements across frequency bands confirmed high inter-band similarity, and temporal loading analysis revealed a systematic gradient of cross-frequency coupling, with delta-band activity showing progressively stronger correspondence toward gamma.
Together, these results establish that large-scale cortical activity is organized into a reproducible vocabulary of spatiotemporal directional elements spanning the full spectrum of neural dynamics, from slow population-level fluctuations to fast gamma rhythms.

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Poster

PSTR115: Optical Methods I

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Title: Multi-level control of orofacial motor output

Authors: *A. G. LIEBERMAN[1], J. S. FELDMAN[1], T. A. MACHADO[1,2];
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Abstract: Orofacial movements including facial expressions, drinking, chewing, and vocalizing are critical for survival. To produce these different behaviors, descending commands from the

cortex exert postsynaptic influence over orofacial premotor circuits in the medulla. These premotor medullary circuits project to the orofacial motor neurons that control the muscles driving orofacial behavior. Many studies have identified key hubs of orofacial motor control across the motor system, but until recently tools to monitor multiple layers of the motor system in tandem did not exist. Furthermore, how cortical and medullary circuits interact to generate different orofacial behaviors across behavioral contexts remains poorly understood.
To address this, we trained head-restrained mice to perform a multi-spout licking task with three trial types requiring either directed licking or lick suppression. As mice behaved, we recorded activity from thousands of neurons across the dorsal cortex using widefield Ca^{2+} imaging. Simultaneously, we recorded putative post-synaptic orofacial premotor and sensory neurons in the medulla using Neuropixels 2.0 probes and tracked orofacial movements using three orthogonal high-speed cameras.
Preliminary results reveal that mice generate context-dependent orofacial movements, including lick bouts that vary in direction, rate, and duration. Analysis of our widefield Ca^{2+} imaging using localized semi-nonnegative matrix factorization (LocaNMF) revealed distinct spatiotemporal patterns of cortical activity that varied with behavioral context. Neuropixels recordings revealed hundreds of putative premotor and sensory medulla units exhibiting diverse activity patterns. We identified rhythmic units tuned to lick bouts, neurons responsive to odor cues, neurons preferentially active during appetitive or consummatory licking, and populations that were suppressed during one or both behavioral epochs. Lastly, a ridge regression encoding model relating single-unit activity to temporally lagged cortical activity patterns revealed changes in cortex-medulla functional coupling across behavioral contexts. Different populations of medulla neurons were best predicted by cortical activity leading or lagging unit activity, consistent with the coexistence of descending motor influences and sensory feedback-related signals within the medulla.Together, our preliminary results shed light on how multiple levels of the motor system govern orofacial movements on a moment-to-moment basis.

Disclosures: A.G. Lieberman: None. **J.S. Feldman:** None. **T.A. Machado:** None.

Poster

PSTR115: Optical Methods I

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Program #/Poster #: PSTR115.19/KK15

Topic: J.04. Physiological Methods

Support: NIH
HHMI

Title: Motivation-dependent communication between cortex and the brainstem

Authors: T. A. MACHADO[1,2], *Y. CHEN[4], M. BEIRAN[5], M. SUBRAMANIAN[1], C. KADUR[4], S. BRADBURY[4], K. NIX[1], B. LIU[4], K. RAJAN[6], K. DEISSEROTH[4,3];
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Stanford, CA; [4]Stanford Univ., Stanford, CA; [5]Columbia Univ., New York, NY; [6]Neurosci., Harvard Univ., Cambridge, MA

Abstract: Medullary premotor circuits are known to generate motor-related patterns of neural activity, yet the population codes that specify distinct actions—and how cortex may shape these medullary codes—remain unclear. We studied these questions in the context of orofacial movements during a task in which mice performed different kinds of licks toward three different waterspouts: pre-reward "appetitive" licks that triggered water, and post-reward "consummatory" licks to collect water, all during 3D kinematic tracking of orofacial behavior. Optogenetic inhibition of cortex (using VGAT-ChR2 mice) first revealed that cortical silencing selectively affected long-distance but not closer licks, suggesting increased involvement of cortex in more dextrous or challenging action types. We then performed population recordings in the motor cortex, and across putative postsynaptic and premotor neuronal populations in the motor-related medulla (a total of 3294 single units were resolved in our dataset across n=9 mice). Analysis of motor-related medulla data revealed a rhythmic phase-based population code for lick direction, and canonical correlation-based decoder analysis revealed that consistent neuronal population codes for lick direction generalized across individual mice. Analysis of correlations between cortex and medulla revealed that these correlations were stronger during appetitive licks than during consummatory licks, a relationship that was supported by both reduced rank regression analysis and multi-region recurrent network modeling. Together, these results support the idea that cortical control over licking behavior is dependent on task context: stronger during more dextrous and motivational "appetitive" licks, and weaker during more rhythmic "consummatory" licks.

Disclosures: T.A. Machado: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Numb Corp. **Y. Chen:** None. **M. Beiran:** None. **M. Subramanian:** None. **C. Kadur:** None. **S. Bradbury:** None. **K. Nix:** None. **B. Liu:** None. **K. Rajan:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree, Maplight, Stellaromics.

Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.20/KK16

Topic: J.04. Physiological Methods

Title: miniOEG: Spatially-resolved optical read/write of neural activity across rodent dorsal cortex during naturalistic behavior

Authors: A. WHITE[1], Y. WANG[2], J. KOCHALKA[1], A. Y. HAO[1], M. LIU[3], B. ESHAGHI GHARAGOZ[1], M. K. LO[1], T. CLANDININ[4], M. Z. LIN[4], ***S. QUIRIN**[5], K. DEISSEROTH[1];

[2]Neurosicence, [3]Bioengineering, [4]Neurobio., [1]Stanford Univ., Stanford, CA; [5]Psychiatry and Behavioral Sci., Stanford Univ., Palo Alto, CA

Abstract: Here we present the miniOEG - a miniaturized macroscope for optoencephalography (OEG) with a 10x10mm field of view that weighs less than 5g and can record and manipulate cell-type specific neural activity across the dorsal cortex of a freely moving mouse. The new scope has the sensitivity to resolve single-trial neural activity, the spatial resolution to capture sub-regional structures, and the spectral resolution to record in multiple colors. The miniOEG capabilities are further enhanced via a second, independent optical path capable of point-and-shoot optogenetic control. Two-color imaging and simultaneous optogenetic stimulation are achievable at frame rates exceeding 40Hz with 256x256 pixel resolution and 80Hz with 128x128 pixel resolution. To validate the imaging capabilities of the miniOEG, we demonstrate retinotopic mapping in visual cortex as well as pan-cortical functional connectivity mapping in freely behaving animals (CaMKIIa-Cre mice expressing GCaMP8m, N = 4). Importantly, after a 3-day habituation protocol, no significant bias of the miniOEG on behavior is observed for many common open-field metrics (i.e. total distance, time in arena center, median velocity, median tortuosity, N = 8, Wilcoxon sign rank, n.s. $p > 0.05$). We demonstrate the optogenetic stimulation capabilities of the miniOEG with spatially resolved (100um illumination precision) random access stimulation of mice expressing GCaMP8m in addition to the potent, red-shifted excitatory opsin rsChRmine (N = 4). Finally, we demonstrate high SNR recording of subthreshold voltage activity across dorsal cortex imaged at 80Hz using the sensitive genetically encoded voltage indicator ASAP7y (expressed with a CaMKIIa promoter, N = 3). The ability thereby enabled, to simultaneously record and control activity across cortex in a cell-type and spatiotemporally specific manner in freely behaving animals, opens the door to unbiased exploration of the endogenous and causal brainwide neural foundations of naturalistic behaviors.

Disclosures: A. White: None. **Y. Wang:** None. **J. Kochalka:** None. **A.Y. Hao:** None. **M. Liu:** None. **B. Eshaghi Gharagoz:** None. **M.K. Lo:** None. **T. Clandinin:** None. **M.Z. Lin:** None. **S. Quirin:** None. **K. Deisseroth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Maplight, Stellaromics. F. Consulting Fees (e.g., advisory boards); Allen Institute, Modulight, RedTree, Maplight, Stellaromics.

Poster

PSTR115: Optical Methods I

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Topic: J.04. Physiological Methods

Support: NIH Grant UG3MH133047
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Title: Illuminating neuromodulatorycircuitryin non-human primates: STARmap-guided optogenetic targeting

Authors: *W. WENDERSKI[1], B. LI[2], Y. Y. CHEN[2], N. ANDINI[1], Y.-P. CHENG[2], S. BRADBURY[2], C. RAMAKRISHNAN[1], R. CHEN[4], E. B. RICHMAN[1], B. ESHAGHI GHARAGOZ[1], L. E. FENNO[2], E. SEIDEMANN[3], K. DEISSEROTH[1];
[1]Bioengineering, Stanford Univ., Stanford, CA; [2]Neurosci., [3]Univ. of Texas at Austin, Austin, TX; [4]Neurolog. Surgery, UCSF, San Francisco, CA

Abstract: Neuromodulatory systems influence the representation, processing, and flow of information in the brain. Functional studies in diverse small vertebrates indicate that neuromodulatory neurons can directly influence sensory processing through projections to telencephalic areas, and may indirectly do so through connections with decision and motor-related cortical areas that send top-down signals to sensory cortex. Sensory responses and perceptual decisions are highly variable and exhibit covariation, possibly due to fluctuations in neuromodulatory inputs to cortical circuits that mediate perceptual decision-making. However, precision tools are lacking for targeting and tuning neuromodulatory circuits during the complex behaviors of primates. To address this need, we adapted STARmap spatial transcriptomics for the non-human primate (NHP) brain. We applied this method to characterize NHP neuromodulatory cell types and to screen virally-delivered DNA elements for selective reporter expression in serotonergic, noradrenergic, dopaminergic or cholinergic neurons. STARmap revealed unprecedented detail in the spatial organization and molecular identities of neuromodulatory neuronal subtypes in NHP brainstem and basal forebrain. Furthermore, this method enabled initial identification of an enhancer with ~85% specificity for dopaminergic neurons in the ventral tegmental area (VTA), and of a second enhancer with initial results suggesting comparable specificity for noradrenergic neurons in the locus coeruleus (LC). The VTA-DA enhancer drove sufficient expression of the excitatory trimeric (pump-like) channelrhodopsin ChRmine to enable optotagging in the awake behaving NHP, driving robust and temporally precise neural activity responses to light. We further utilized STARmap and single nucleus RNA-sequencing to identify neuronal subtypes within NHP sensorimotor cortex which may mediate neuromodulatory effects on cortical processing neocortex by virtue of specific neuromodulator receptor expression. This comprehensive characterization of NHP neuromodulatory neurons, combined with highly specific viral genetic tools to functionally access this circuitry, may help empower causal studies for deeper understanding of neuromodulatory processing in the primate brain.

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Poster

PSTR115: Optical Methods I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR115.22/KK18

Topic: J.04. Physiological Methods

Title: Surpassing the depth limit imposed by out-of-focus fluorescence in two-photon microscopy

Authors: *D. M. FARINELLA[1], P. KARA[2];
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Abstract: Two-photon microscopy (2PM) is widely used for micron-scale fluorescence imaging in scattering tissue such as the brain, but its penetration depth is ultimately limited when out-of-focus fluorescence accumulates and the signal-to-background ratio (SBR) approaches unity. Three-photon microscopy (3PM) extends reachable imaging depth by combining longer excitation wavelengths, which reduce scattering in tissue, with higher-order excitation, which suppresses out-of-focus fluorescence and improves SBR at depth. However, 3PM requires substantially higher pulse energies to generate usable fluorescence at depth, increasing the risk of peak-intensity-dependent photodamage and average-power-dependent tissue heating, thereby forcing tradeoffs among imaging speed, field of view, and imaging duration. A longstanding goal is therefore to retain the excitation efficiency and broad utility of 2PM while suppressing the out-of-focus fluorescence that limits its penetration depth. Recent non-degenerate two-photon approaches have reduced out-of-focus fluorescence by using spatially distinct excitation paths to localize nonlinear excitation near the focal plane, but these spatially distinct excitation schemes can achieve background suppression at the cost of effective excitation numerical aperture and excitation efficiency, limiting deeper imaging in practice. Here, we introduce a novel non-degenerate two-photon excitation strategy designed to suppress out-of-focus fluorescence while preserving access to the full excitation numerical aperture of the objective. By producing temporal isolation of the excitation pulses outside the focal region while preserving efficient two-photon excitation at the focus, this approach is designed to reduce distributed background generated outside the focal volume. Because out-of-focus fluorescence becomes increasingly dominant with depth, the predicted benefit of this strategy increases with optical depth. This strategy directly targets the depth-limiting background in 2PM while retaining substantially lower pulse-energy demands than 3PM.

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Poster

PSTR115: Optical Methods I

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Program #/Poster #: PSTR115.23/KK19

Topic: J.04. Physiological Methods

Support: NIH Grant R01 NS140244

Title: A microscope- and model-agnostic framework for real-time denoising in photon-limited two-photon and three-photon imaging

Authors: *N. A. IYER[1], C. NGUYEN[2], C. VALLEROY[3], D. FARINELLA[5], S. SWIGGUM[6], P. KARA[4];
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Abstract: Multiphoton fluorescence imaging is often constrained by detected photons when imaging at depth, reducing excitation power, increasing frame rate, or preserving large fields of view. In two-photon microscopy, decrease in detected photons due to poor expression, low fluorophore brightness, or increasing depth in the case of sparse labelling can make segmentation and activity extraction unreliable. While three-photon imaging extends reachable depth by reducing out-of-focus fluorescence through higher-order excitation, useful fluorescence at depth requires higher pulse energies, lower repetition rates, and remaining below limits imposed by peak-intensity-dependent photodamage and average-power-dependent tissue heating. These constraints create a photon-limited regime in which noisy images, weak transients, and poor segmentation limit biological readouts. To address these problems, we developed a microscope- and model-agnostic real-time denoising framework for photon-limited multiphoton imaging. The framework decouples microscope acquisition from neural-network inference using shared-memory adapters and deploys denoising models as ONNX/TensorRT inference engines, allowing the same runtime to support multiple acquisition environments and denoising architectures. We benchmark multiple denoising architectures, including DeepCAD-RT, FAST, SUPPORT, and a causal ConvGRU-based model. The causal model was optimized for low-frame-rate three-photon imaging and denoises each frame using only the current input and its recurrent hidden state. This minimizes algorithmic delay during live imaging, particularly in low frame rate regimes where acausal methods introduce significant algorithmic latency regardless of inference speed. We evaluated the system using NAOMi simulations, simultaneous photon-split validation experiments, and low-signal three-photon imaging in the visual cortex. The framework achieved real-time performance with median end-to-end latency below 10 ms under benchmark conditions. Across simulated and photon-split datasets, denoising appeared to improve soma segmentation, fluorescence trace fidelity, and event detectability while maintaining performance comparable to non-causal denoising approaches. In multiphoton in vivo recordings from visual cortex, real-time denoising appeared to recover visually evoked activity in low-photon conditions. These results show that real-time causal denoising can improve biological signal recovery under photon-limited imaging conditions and provide a flexible path for integrating deep-learning denoisers into live imaging workflows.

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Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.01/KK20

Topic: J.04. Physiological Methods

Support: NIH R01NS13344103

Title: In vivo time-lapse imaging reveals differential activity-induced regulation of proteasome activity in subcellular regions of the optic tectum in Xenopus laevis tadpoles

Authors: J. LIN[1], **B. BAAH KONADU, OD**[2], *H. HE[1];
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Abstract: The proteasome is a major organelle responsible for protein degradation in neurons and has been implicated in the regulation of signal transduction and activity-dependent plasticity mechanisms that are essential for normal neuronal function. However, our understanding of the regulation of proteasome activity in the brain is limited by currently available assays and tools. Here, we used a fluorogenic substrate-based probe, TAS1, to directly monitor proteasome activity in the brain of *Xenopus laevis* tadpoles with time-lapse two-photon microscopy. With the spatial resolution enabled by *in vivo* imaging, our data revealed a significant difference in proteasome activity between brain regions enriched in neuronal soma versus neuropil under both basal and pharmacologically stimulated conditions, suggesting differential activity-induced regulation of proteasome activity across neuronal subcellular compartments. These results demonstrate the feasibility of using TAS1 to track proteasome activity *in vivo* and provide new evidence for differential regulation of proteasome activity in different subcellular compartments of neurons in the intact neural circuit.

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

Poster

PSTR116: Optical Methods II

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Program #/Poster #: PSTR116.02/KK21

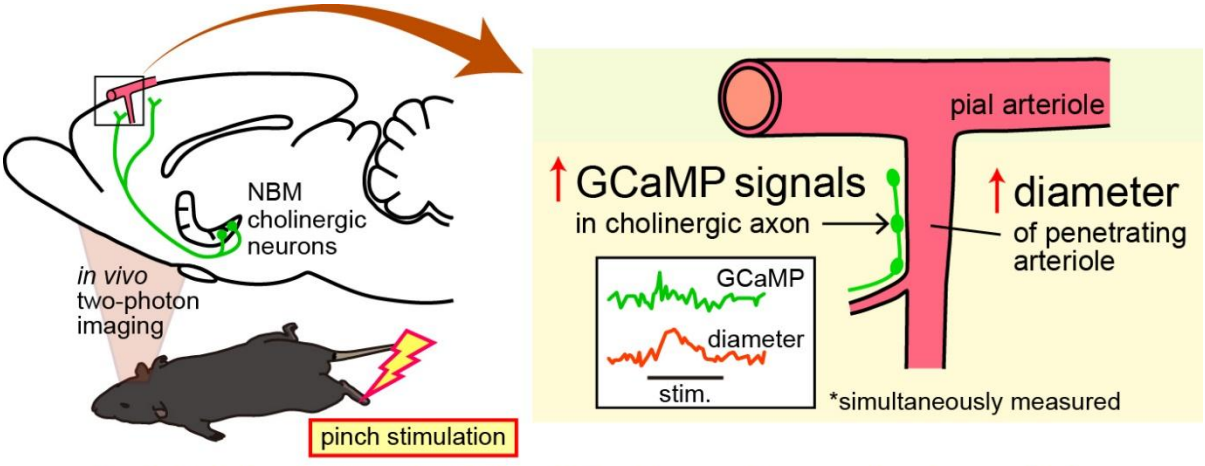
Topic: J.04. Physiological Methods

Support: Tsumura & Co.

Title: Simultaneous in vivo imaging of Ca^{2+} signals in periarteriolar cholinergic axonal varicosities and cerebral arteriole dynamics in urethane-anesthetized mice

Authors: *N. WATANABE, H. HOTTA;
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Abstract: Cholinergic neurons in the nucleus basalis of Meynert (NBM) project widely to the cerebral cortex and are implicated in cognitive function and cerebrovascular regulation. Although cholinergic axons are reportedly distributed around the cerebrovasculature, their functional relationship with arteriolar dynamics remains unclear. Therefore, we aimed to establish a method for simultaneous *in vivo* imaging of NBM cholinergic axon activity and cerebral arteriole dynamics. Experiments were performed in male mice. Under isoflurane anesthesia, an adeno-associated virus (AAV) vector carrying the ChAT promoter to target cholinergic cells was injected into the right NBM to express jGCaMP8s. Three to four weeks later, blood plasma was fluorescently labeled and the right frontal cortex was imaged using two-photon microscopy under urethane anesthesia. Pinch stimulation, known to increase NBM activity and cortical blood flow, was applied to the left hindpaw, and changes in Ca^{2+} fluorescence intensity and arteriole diameter were measured. Three-dimensional imaging revealed bead-shaped Ca^{2+} signals around arterioles (0.33-4.89 μm from the arteriole) at depths up to 40 μm below the cortical surface in all AAV-injected mice. Two-dimensional time-series imaging demonstrated that pinch stimulation induced transient Ca^{2+} increases and arteriole dilation. Notably, the Ca^{2+} peak preceded the arteriole diameter peak by ~2.1 s. Cross-correlation analysis supported this temporal relationship. Additionally, linear regression analysis showed that the magnitude of Ca^{2+} changes was significantly correlated with that of arteriole diameter changes ($R^2 = 0.73$, $p = 0.0016$). In conclusion, we established an experimental approach for simultaneous *in vivo* imaging of periarteriolar cholinergic axon activity and cerebral arteriolar dynamics. This approach revealed a temporal and quantitative relationship between periarteriolar cholinergic axon activity and arteriolar dynamics during pinch stimulation.



Periarteriolar cholinergic Ca^{2+} activity shows a temporal and quantitative relationship with arteriole diameter changes.

Disclosures: N. Watanabe: None. **H. Hotta:** 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.; Tsumura & Co.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

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Topic: J.04. Physiological Methods

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JSPS KAKENHI JP25K03273
JSPS KAKENHI JP24H01497
JSPS KAKENHI JP24K03085
JSPS KAKENHI JP24K22259
JSPS KAKENHI JP23K28178
JSPS KAKENHI JP23H03488
JSPS KAKENHI JP23K18485
JSPS KAKENHI JP22H05698
JSPS KAKENHI JP23K21713
JSPS KAKENHI JP23K21755
JSPS KAKENHI JP24K18267
JSPS KAKENHI JP21K15247

Title: Wide-field Voltage-Sensitive Dye Imaging Reveals Fast Functional Recruitment of the DMS Concurrent with ACC Activity in Coronal Mouse Brain Slices

Authors: *T. TOMINAGA[1,2], M. TAKETOSHI[1], Y. TOMINAGA[1,3];
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Abstract: The anterior cingulate cortex (ACC) is implicated in cognitive control and action selection, and its projection to the dorsomedial striatum (DMS) is considered an important substrate for goal-directed behavior. Although ACC-to-DMS projections are anatomically well documented, the fast mesoscale dynamics by which ACC activity is accompanied by DMS recruitment remain insufficiently characterized. Wide-field voltage-sensitive dye (VSD; Di-4-ANEPPS) imaging provides millisecond-scale temporal resolution and a broad, stable field of view, enabling simultaneous monitoring of ACC activity and DMS membrane potential signals in coronal brain slices.We systematically prepared acute coronal mouse brain slices across multiple bregma levels and recorded VSD signals at 1 ms per frame during focal electrical stimulation. Because the imaging field covered medial frontal cortical regions and the DMS in the same slice, stimulus-evoked ACC activity, cortical propagation, and DMS responses could be

evaluated without repositioning or sequential recordings. Stimulation that recruited ACC activity, either through cortical input or direct ACC stimulation, was accompanied by a depolarizing response in the DMS. DMS activation coincided with ACC activity, particularly when activation reached the middle ACC region, and was most prominent in anterior slices, suggesting a rostrocaudal dependence of functional DMS recruitment. When stimulation was delivered near the midline to layer 2/3 at the dorsoventral midpoint of Cg1, DMS activation emerged in the same imaging frame as the ACC response. Thus, stimulus-to-DMS latency was not operationally definable under this condition, because ACC activity propagated from the stimulation site while the DMS response was detected within the same temporal sampling interval.In the same slices, DMS stimulation evoked a response in the corresponding ACC subregion, consistent with activation of corticostriatal fibers, potentially including antidromic recruitment of ACC neurons projecting to the DMS. DMS responses showed similarly fast dynamics across cortical input, contralateral propagation, and direct ACC stimulation.Collectively, these results demonstrate that wide-field VSD imaging can detect fast DMS signals concurrent with ACC activity in coronal mouse brain slices, highlighting its value for resolving mesoscale corticostriatal dynamics with stable, simultaneous optical recordings.

Disclosures: T. Tominaga: None. **M. Taketoshi:** None. **Y. Tominaga:** None.

Poster

PSTR116: Optical Methods II

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Program #/Poster #: PSTR116.04/KK23

Topic: J.04. Physiological Methods

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JSPS KAKENHI JP21K15247
JSPS KAKENHI JP25H01156
JSPS KAKENHI JP25K03273
JSPS KAKENHI JP24H01497
JSPS KAKENHI JP24K03085
JSPS KAKENHI JP24K22259
JSPS KAKENHI JP23K28178
JSPS KAKENHI JP23H03488
JSPS KAKENHI JP23K18485
JSPS KAKENHI JP22H05698
JSPS KAKENHI JP23K21713
JSPS KAKENHI JP23K21755

Title: An Optimized Pixel-wise VSD Imaging Assay for Detecting Subtle Hippocampal Circuit Alterations Induced by Bisphenol Analogs

Authors: *Y. TOMINAGA[1,3], M. TAKETOSHI[1], K. TANEMURA[4], T. TOMINAGA[1,2];
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Abstract: Exposure to environmental chemicals, including bisphenol A (BPA) and its phenolic analogs, may perturb neural circuit function in subtle and spatially distributed ways. Such alterations can be difficult to detect with conventional single-cell recordings alone, requiring approaches that preserve both regional circuit organization and fine spatial resolution. To address this need, we developed an optimized voltage-sensitive dye (VSD) imaging pipeline for acute mouse hippocampal slices. This approach measures stimulus-evoked changes in VSD fluorescence (dF/F0) across the hippocampal network and integrates ROI-based response quantification with Benjamini-Hochberg false discovery rate-corrected pixel-wise statistical maps (BH-FDR), enabling detection of spatially distributed compound effects while controlling for multiple comparisons.
We applied this pipeline to compare the acute effects of BPA, 4,4'-butylidenebisphenol (BB), and 2,2'-methylenebisphenol (MB) with control slices. Synaptic responses were quantified using peak amplitude (PEAK) and time-integrated magnitude (SUM) of dF/F0 across the hippocampal trisynaptic pathways, including CA1, CA3, and the dentate gyrus (DG). Imaging was performed under low- and high-intensity stimulation, both under baseline conditions (normal ACSF) and after disinhibition with the GABA(A) receptor antagonist gabazine (+GZ).
The bisphenol analogs BB and MB produced statistically robust and spatially widespread reductions in circuit outputs across multiple ROI-defined pathways, whereas BPA showed fewer supported effects. Importantly, these alterations depended on pathway, subfield, animal age (2-week juvenile versus 8-week young adult), response metric, stimulation intensity, and inhibitory state. More selective and localized suppression was observed in juvenile slices, particularly when evaluated using the SUM metric under disinhibited conditions, suggesting that disinhibition can unmask latent circuit defects.
These findings demonstrate that integrating macro-level ROI summaries with micro-level BH-FDR-corrected pixel-wise statistical maps provides a sensitive framework for detecting condition-dependent circuit alterations in hippocampal networks. Our results further indicate that BPA-related analogs can differ substantially from BPA itself in their acute functional effects on mammalian hippocampal circuitry, underscoring the need for spatially resolved functional profiling in environmental neurotoxicity screening.

Disclosures: Y. Tominaga: None. **M. Taketoshi:** None. **K. Tanemura:** None. **T. Tominaga:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.05/KK24

Topic: J.04. Physiological Methods

Title: Development of a video-synchronized in vivo fluorescence lifetime photometry system for 24-hour monitoring of neuromodulation and intracellular signaling in the mouse brain

Authors: *M. H. SHAH, J. LEE, A. HOLDER, D. L. HAGGERTY, C. B. DARDEN, D. M. LOVINGER;
The Lab. for Integrative Neurosci., Natl. Inst. on Alcohol Abuse and Alcoholism (NIAAA) / Natl. Inst. of Hlth. (NIH), Rockville, MD

Abstract: Quantifying in vivo neuromodulation aligned with behavioral state changes over a 24-hour timescale is essential for understanding how circadian rhythms shape brain signaling and relate to changes in behavioral output. Existing neurochemical monitoring methods, including microdialysis, fast-scan cyclic voltammetry, and conventional fiber photometry, are limited in their ability to provide continuous, high-resolution recordings of neuromodulation over extended periods of time. In parallel, existing high-resolution video-based behavior-tracking tools, such as DeepLabCut, have slow inference times when analyzing locomotion state changes across dense video recordings. In this study, we developed a video-synchronized in vivo fluorescence lifetime photometry platform capable of 24 hour monitoring of neuromodulation and behavior in freely moving mice by leveraging (1) a custom time-correlated single photon counting (TCSPC) fiber photometry system capable of long-term neuromodulatory recordings from intensity-based biosensors (e.g., GRAB-DA) and fluorescence lifetime-based biosensors (e.g., G-CHAMP), using low-power laser excitation and highly photon-sensitive hybrid detectors; and (2) an open-source mouse pose estimator software, SqueakPose, capable of extremely fast inference speeds across lengthy videos through its You Only Look Once (YOLO) machine vision architecture. To bridge these systems into a platform, a custom Python interface first synchronizes TCSPC acquisition with the frame capture of a near-infrared USB camera via Arduino TTL signaling during a 24-hour recording session. These TCSPC-synchronized videos are then streamlined into SqueakPose for locomotion extraction. We first validated our platform by tracking striatal dopamine and cAMP release, measured with GRAB-DA and G-CHAMP biosensors, respectively, alongside behavioral state changes over 1-3 hours following pharmacological manipulations, including dopamine D1/D2 receptor antagonists and ethanol. We then used the platform to continuously monitor dopamine and cAMP signaling in striatal D2 receptor-expressing medium spiny neurons, alongside behavior, during free-roaming conditions over 24 hours. We will use this platform to further quantify striatal neurotransmitter dynamics, including adenosine release and related behavioral state changes, across similar circadian timescales. Through our custom platform approach, we provide a scalable framework for 24-hour, temporally aligned analysis of neuromodulatory signaling and behavior, enabling future studies of how circadian rhythms shape brain signaling and behavioral output.

Disclosures: M.H. Shah: None. **J. Lee:** None. **A. Holder:** None. **D.L. Haggerty:** None. **C.B. Darden:** None. **D.M. Lovinger:** None.

Poster

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Program #/Poster #: PSTR116.06/KK25

Topic: J.04. Physiological Methods

Support: NIH Grant 1R61xMH138705-01

Title: fNIRS-fMRI Reliability for Motor and Social Perception Paradigms: Validation of fNIRS Against fMRI

Authors: *J. A. NOAH[1], X. ZHANG[1], D. PURUSHOTHAMAN[3], S. SANCHEZ-ALONSO[4], V. L. GRACCO[7], D. J. OSTRY[8], N. RAO[5], M. TIEDE[6], J. HIRSCH[2];
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Abstract: Functional near-infrared spectroscopy (fNIRS) holds significant potential for investigations of naturalistic tasks in developmental and social neuroscience, yet its reliability relative to fMRI requires systematic validation beyond fiducial tasks. We compared hemodynamic responses recorded with a Shimadzu fNIRS system against BOLD signal acquired on a Siemens MAGNETOM Prisma 3T scanner using two paradigms. First, a lateralized finger-thumb tapping task (left and right hand) engaged primary sensorimotor cortex, providing a spatially focal benchmark. Second, dynamic face stimuli obtained from Pitcher, Dilks, Saxe, Triantafyllou & Kanwisher (2011) targeted the posterior superior temporal sulcus (pSTS), a region critically selective for dynamic facial information compared to other types of motion or static face processing. fNIRS and fMRI demonstrated strong reliability across both conditions. The motor task showed robust correspondence in hemispheric lateralization. For the social perception condition which had participants watch pre-recorded videos of the faces of children smiling, moving and chewing, fNIRS reliably detected activity in the visual cortex, lateral-occipital cortex, superior and middle temporal lobes as well as multiple sites in the pSTS during dynamic face processing, with signal correspondence confirmed against BOLD. Critically, fMRI constrains social stimuli to camera-recorded video, eliminating two defining features of natural social exchange: gaze reciprocity, as eye contact cannot be returned by a recorded face, and facial mimicry, as a video stimulus cannot respond to or mirror the participant's own facial expressions. fNIRS imposes neither limitation, permitting live face-to-face interaction in which gaze and facial affect are fully contingent and bidirectional. This ecological advantage is particularly consequential for studying social perception in populations where naturalistic social exchange is central to the research question. These findings validate fNIRS as a platform for developmental contexts where fMRI is impractical and ecological validity is essential.
References Pitcher, D., Dilks, D. D., Saxe, R. R., Triantafyllou, C., & Kanwisher, N. (2011). Differential selectivity for dynamic versus static information in face-selective cortical regions. *NeuroImage*, *56*(4), 2356-2363. https://doi.org/10.1016/j.neuroimage.2011.03.067

Disclosures: J.A. Noah: None. **X. Zhang:** None. **D. Purushothaman:** None. **S. Sanchez-Alonso:** None. **V.L. Gracco:** None. **D.J. Ostry:** None. **N. Rao:** None. **M. Tiede:** None. **J. Hirsch:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.07/KK26

Topic: J.04. Physiological Methods

Support: IVIM Technology

Title: Real-time imaing of neurovascular and microglial dynamics during locomotion in awake mice using intravital microscopy

Authors: *J. LEE[1], P. KIM[2,1];
[1]IVIM Technol., Daejeon, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract: Brain function is tightly coupled with complex interactions among neurons, glia, and vasculature; yet, investigating these processes in a physiological state remains challenging due to anesthesia-induced artifacts. In this study, we established a high-resolution, long-term intravital imaging platform using both confocal and two-photon microscopy to visualize brain dynamics in awake, head-fixed mice. To overcome the optical opacity of the skull and ensure stable imaging, we performed cranial window implantation, which provided clear optical access to the cortex. This platform was integrated with a linear treadmill, allowing mice to engage in locomotion. We utilized separate Thy1-GCaMP6f and CX3CR1-EGFP transgenic mouse lines to monitor neuronal calcium activity and microglial surveillance, respectively, combined with intravenous administration of dextran to monitor real-time vascular dynamics and CD31 labeling to delineate endothelial structures. This multi-modal imaging approach allowed us to capture the real-time modulation of neurovascular coupling and microglial process motility in response to locomotion. Our data demonstrates that both spontaneous and treadmill-induced locomotor activity trigger locomotion-dependent changes in blood flow and vascular diameter, which are precisely synchronized with neuronal calcium transients. Furthermore, we noted that microglial processes frequently exhibited positional adjustments in proximity to activated vascular regions during movement. To overcome signal-to-noise limitations inherent in awake imaging, we applied an AI-based image denoiser, enabling high-fidelity visualization of fine structural and functional changes. Our findings provide direct visual evidence of the intimate link between behavioral states and brain homeostasis, establishing our platform as a powerful tool for investigating the pathophysiology of neurological disorders under truly physiological conditions.

Disclosures: J. Lee: None.

Poster

PSTR116: Optical Methods II

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Topic: J.04. Physiological Methods

Support: 2022R52033
2025C01137

Title: Online analyzing neural population activities from single-photon calcium images bypassing trace extraction

Authors: ***Z. HUANG**[1], M. LI[1], R. WANG[2], G. WAN[1], Y. YANG[1], H. ZHANG[1], Y. XU[2], S. ZHANG[1];
[1]Zhejiang Univ., Hangzhou, China; [2]Westlake Univ., Hangzhou, China

Abstract: Single-photon calcium imaging enables large-scale recordings of neuronal population activity during natural behavior, but conventional ROI-based source extraction remains a major bottleneck for online analysis. By requiring offline identification of neuronal footprints and fluorescence traces, these workflows cannot readily support real-time processing and may discard informative field-of-view signals outside curated ROIs. Here, we developed an end-to-end analysis workflow that predicts continuous lever pressure directly from foreground-enhanced miniscope image sequences, eliminating source extraction during prediction. Three mice performed auditory-cued lever pressing while a head-mounted miniscope recorded layer 2/3 motor-cortex calcium movies at 20 Hz over six sessions. Miniscope movies were motion corrected using subpixel image registration, then foreground-enhanced with anisotropic diffusion filtering and morphological opening. Lever pressure was estimated from five-frame spatiotemporal samples with a two-frame output delay using a supervised regressor combining a 3D residual-convolutional encoder and a recurrent temporal module. Performance was assessed by five-fold cross-validation and compared with trace-based workflows using MIN1PIPE or EXTRACT followed by the same temporal module. The image-based workflow markedly reduced processing time and achieved frame-rate-compatible processing for 20-Hz online analysis. It processed 1000-frame videos in ~7 s, compared with 58-233 s for EXTRACT and 903 s on average for MIN1PIPE (n=10 videos, $p<0.01$). In a streaming simulation, the full pipeline required 21.8 ms per sample, below the 50 ms frame interval. Importantly, this speed gain did not compromise accuracy. Image-based prediction produced higher correlations with measured pressure and lower mean squared errors than both trace-based workflows across all six sessions (Wilcoxon signed-rank tests, $p<0.05$). Moreover, small local fluorescence components and background-derived images also improved predictive performance, suggesting that behaviorally informative signals can extend beyond curated ROIs. Overall, this end-to-end image-based workflow combined rapid processing, accurate pressure prediction, and improved retention of behaviorally informative field-of-view signals. Together with a custom behavioral chamber and synchronized acquisition-control software, this workflow provides a platform for real-time feedback paradigms based on single-photon calcium imaging.

Disclosures: Z. Huang: None. **M. Li:** None. **R. Wang:** None. **G. Wan:** None. **Y. Yang:** None. **H. Zhang:** None. **Y. Xu:** None. **S. Zhang:** None.

Poster

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Program #/Poster #: PSTR116.09/KK28

Topic: J.04. Physiological Methods

Support: JP25K24569

Title: Integrated Ultra-Compact CMOS Imaging and Optical Stimulation Devices Enable an All-Optical Therapeutic Approach for Alcohol Addiction

Authors: *Y. OHTA[1], V. G. CASTILLO[1], Y. SUNAGA[1], M. OHSAWA[2], **J. OHTA**[1]; [1]Nara Inst. of Sci. and Technol., Ikoma, Japan; [2]Systems Pharmacol., Teikyo Univ., Tokyo, Japan

Abstract: Neurological disorders are commonly treated with pharmacological agents or electrical stimulation, approaches that often provide only symptomatic relief. Advances in genetic engineering now enable neuron-specific monitoring and manipulation of neural circuits with optical technologies, offering new opportunities for therapies based on targeted modulation of synaptic plasticity. We have developed a brain-implantable ultra-compact CMOS (Complementary Metal-Oxide-Semiconductor) imaging sensor (*i*-CIS) device and a miniaturized optical stimulation device incorporating a micro-LED. By combining these technologies, we aim to establish an all-optical platform for both diagnosis and treatment.To evaluate this approach, we targeted alcohol addiction, which is closely associated with mesolimbic dopamine signaling. DAT-Cre mice received AAV-flex-ChRmine injections into the ventral tegmental area (VTA) to enable dopamine neuron-specific optical stimulation. To monitor neurotransmitter dynamics, AAV-GRABDA or AAV-iGluSnFR was injected into the nucleus accumbens shell (NAcShell). An *i*-CIS device was implanted into the NAcShell, and an optical stimulation device equipped with a micro-LED with a central wavelength of 590 nm was implanted into the VTA. Mice received intraperitoneal alcohol administration for three consecutive days. On day 3, optical stimulation was delivered to the VTA as a therapeutic intervention. On day 4, low-intensity stimulation insufficient to induce synaptic plasticity was applied to evaluate treatment-related circuit changes. Control groups received saline and/or no optical stimulation. Treatment efficacy was assessed using a two-bottle preference test, and neural plasticity was evaluated by immunohistochemistry. Fluorescence imaging revealed alcohol-dependent changes in neurotransmitter dynamics within the NAcShell. Dopamine neuron-specific stimulation of the VTA modulated these signals and reduced alcohol preference compared with controls. Histological analyses further supported stimulation-induced plasticity in reward-related circuits. These findings demonstrate the feasibility of an integrated all-optical platform for diagnosis and treatment of alcohol addiction. This phototherapeutic strategy may also be applicable to other neurological and neuropsychiatric disorders, including chronic pain, epilepsy, depression, and Parkinson's disease.

Disclosures: Y. Ohta: None. **V.G. Castillo:** None. **Y. Sunaga:** None. **M. Ohsawa:** None. **J. Ohta:** None.

Poster

PSTR116: Optical Methods II

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Program #/Poster #: PSTR116.10/KK29

Topic: J.04. Physiological Methods

Support: Stanford Knight Initiative for Brain Resilience
HHMI

Title: Linking neural dynamics to cellular identities with TRU-FACT: applications across brain areas in head-fixed and freely behaving animals.

Authors: *X. JIANG[1], X. SUN[1], L. WANG[1], G. CHATTREE[2], Y. JIANG[3], A. CETIN[1], X. CAI[1], R. T. CHRAPKIEWICZ[4], F. DINC[5], B. KURTKAYA[6], Y. ZHANG[1], M. J. SCHNITZER[7];
[1]Stanford Univ., Palo Alto, CA; [2]Stanford Univ., Mountain View, CA; [3]Electrical Engin., [4]Stanford Univ., Stanford, CA; [5]UC Santa Barbara, Santa Barbara, CA; [6]Koc Univ., Istanbul, Turkey; [7]Depts. Biol. & Applied Physics, Stanford University, HHMI, Stanford, CA

Abstract: A central challenge in neuroscience is linking the activity of individual cells as recorded in live animals to their molecular, anatomical, and connectivity attributes. We developed the TRU-FACT (Total Registration Under Functional Activity, Connectivity, and Transcriptomics) pipeline to address this challenge by enabling registrations of large populations of individual cells across intravital imaging, connectivity mapping, and spatial biology datasets. By combining tissue-preserving optomechanical experimental workflows with the Soma-print algorithm, a computational method for registering individual cells across image sets, TRU-FACT provides a general framework for connecting neural activity patterns with cellular identities. Here, as exemplars, we describe two distinct biological applications of TRU-FACT. First, using conventional two-photon microscopy, we applied TRU-FACT to study the calcium dynamics of large populations of motor cortical neurons in head-fixed behaving mice. We studied both healthy mice and a mouse model of Parkinson's disease (PD). Our data revealed cell-type- and circuit-specific activity changes that were associated with the disease state and that provide a foundation for testing targeted strategies to restore function in the affected neural populations. Second, leveraging TRU-FACT's applicability to the study of freely moving animals and the use of GRIN lenses to image deep brain areas, we used TRU-FACT to examine how prefrontal cortical neurons contribute to systems consolidation of a contextual fear memory. Using a miniature two-photon microscope, we longitudinally recorded the activity of prefrontal cortical neurons and characterized their specific long-range projection targets and distinct molecular profiles.
Jointly, these applications illustrate that TRU-FACT bridges functional imaging, circuit anatomy, and molecular profiling at single-cell resolution and will be useful for the study of diverse biological questions. More broadly, our work establishes a scalable approach for identifying the molecular and circuit identities of functionally defined neurons, allowing more

precise mechanistic studies of neural computation, behavior, and disease. By revealing how specific neural populations are altered in pathological states, TRU-FACT also provides a path toward more targeted, cell-type-specific therapeutic strategies for circuit disorders.

Disclosures: X. Jiang: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent assigned to Stanford. **X. Sun:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent assigned to Stanford. **L. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent assigned to Stanford. **G. Chattree:** None. **Y. Jiang:** None. **A. Cetin:** None. **X. Cai:** None. **R.T. Chrapkiewicz:** None. **F. Dinc:** None. **B. Kurtkaya:** None. **Y. Zhang:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent assigned to Stanford.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.11/KK30

Topic: J.04. Physiological Methods

Title: Neurological pupillary index (NPi) as a predictor of functional outcome in patients with acute ischemic cerebrovascular disease

Authors: E. ROCHA[1], G. TORRES[2], D. ORTEGA DOMINGUEZ[1], J. CRUZ[1], J. ZEPEDA PÉREZ[1], G. CARDENAS[3], ***J. MARTINEZ-LAZCANO**[4];
[1]Intensive Care Unit, [2]Lab. of Mol. Neuropharm. and Nanotechnology, [3]Neurol., Inst. Nacional de Neurología y Neurocirugía MVS, Mexico City, Mexico; [4]Lab. of Mol. Neuropharm. and Nanotechnology, Inst. Nacional de Neurología y Neurocirugía MVS, Mexico D.F., Mexico

Abstract: The neurological pupillary index (NPi) is an important component of the neurological assessment of patients with acute brain injury. An abnormal NPi is generally considered an early sign of neurological deterioration and worsening of the injury. Therefore, we evaluated the value of automated NPi in predicting functional outcome in stroke patients. Objective: To evaluate the relationship between the neurological pupillary index (NPi) and outcome in patients with ischemic stroke treated at the INNN (National Institute of Neurology and Neurosurgery). Material and Methods: Observational, analytical, retrospective study. Non-probability convenience sampling. Sample: N=60 patients, n=30 controls; n=30 stroke-i. CI: Patients over 18 years of age admitted to the emergency department or ICU with a diagnosis of stroke-I and NPi measurement on admission, NIHSS, mRS, and/or GOSE scores recorded, and functional outcome data at discharge. CE: Patients with a history of surgery or ocular injury, use of ocular medications, neurodegenerative or structural diseases with chronic brainstem involvement, or death. CElim. Late identification of an alternative diagnosis (e.g., encephalitis, posterior

reversible encephalopathic syndrome without ischemia, non-epileptic seizures) that invalidates the original classification. Results: Sixty-one patients were analyzed: 37 women (60.6%) and 24 men (39.3%), 30 controls, and 31 with stroke-i. No association was observed between the NPI, GOSE, and mRS scores in either group. In the controls, the correlation between GOSE and NPI was nearly nil (r = 0.04-0.06), whereas the correlation with mRS was slightly better (r = 0.03-0.15). In the case group, the correlations between GOSE and NPI (r = -0.12 and -0.18) were low, as were the correlations between mRS and NPI (r = 0.08 and 0.096). Based on these data, we concluded that, in the study population, functional outcome is not associated with NPI. The SOFA mortality prognostic scale showed a negative correlation with GOSE (r = -0.43), meaning that greater organ dysfunction was associated with a worse functional outcome. The mRS correlation was 0.54, indicating that greater organ dysfunction was associated with greater functional impairment. Conclusions: When comparing our study with existing literature, it differs in the type of population studied, primarily in patients with traumatic brain injury, subarachnoid hemorrhage, and anoxic-ischemic injury, where there is direct involvement of the brainstem in the initial stages. In stroke injury, this could occur in advanced stages when there is established secondary injury with malignant cerebral infarction and severe cerebral edema.

Disclosures: E. Rocha: None. **G. Torres:** None. **D. Ortega Dominguez:** None. **J. Cruz:** None. **J. Zepeda Pérez:** None. **G. Cardenas:** None. **J. Martinez-Lazcano:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.12/KK31

Topic: J.04. Physiological Methods

Support: NIH Intramural Research Program

Title: Evidence for Buffering of Endogenous Dopamine by Commonly Used Sensors

Authors: *J. SHIN[1], S. R. WHITE[2], S. LEE[3], A. CARR[3], V. A. ALVAREZ[3];
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Abstract: Genetically encoded dopamine sensors, such as dLight and GRAB-DA versions, have transformed how we study dopamine dynamics by enabling high spatiotemporal resolution optical recordings in neural tissue. These sensors are built from the dopamine-binding domain of the native dopamine receptor (dLight sensors from D1 receptor and GRAB-DA from D2 receptor). Therefore, the sensors can in principle compete with native receptors for extracellular dopamine, a phenomenon known as ligand buffering. Despite this recognized potential caveat, direct experimental evidence of sensors buffering endogenous dopamine away from native receptors are missing and, if so, any strategies to mitigate buffering remain limited.
In this study we investigate possible dopamine buffering abilities of the dopamine sensor

dLight1.3B. We measured striatal dopamine signals with the sensor via photometry while simultaneously recording dopamine with electrochemical currents via fast-scan cyclic voltammetry (FSCV). In ex vivo brain slices from mice, we assessed the effect of blocking dopamine binding to dLight1.3 with the D1R competitive antagonist SCH23390 (2 μM) and how it impacted the dopamine signals measured with FSCV.
As expected, SCH23390 blocked the evoked fluorescent signals measured with dLight1.3b. Interestingly, the antagonist significantly increased the evoked dopamine signals measured simultaneously with FSCV, which may be evidence for dLight1.3 buffering of DA extracellular levels. The evoked dopamine signals increased by 300 ± 53.3% of pre-antagonist level measured by FSCV. This enhancement by D1-like antagonist was only seen in brain slices expressing dLight1.3B sensor. Antagonist application had no effect on evoked FSCV signals when dLight1.3 was not expressed in the tissue (95.2 ± 0.9% of baseline levels), indicating SCH23390 itself does not alter dopamine release or reuptake.
These findings show that pharmacological displacement of dopamine from the sensor binding site can enhance dopamine signals measured by other methods. The findings provide evidence that genetically encoded sensors can mediate dopamine buffering under conditions commonly used by neuroscientists. These findings have important implications for our interpretation of dopamine signals using sensors.

Disclosures: J. Shin: None. **S.R. White:** None. **S. Lee:** None. **A. Carr:** None. **V.A. Alvarez:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.13/KK32

Topic: J.04. Physiological Methods

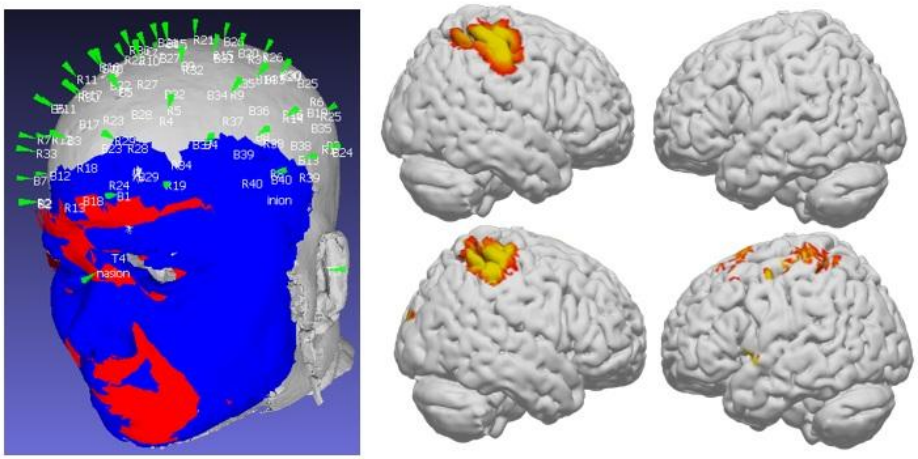
Support: R61xMH138705-01

Title: Comparing fNIRS and fMRI with Surface-Based Registration and Hyper-Resolution Analysis

Authors: *X. ZHANG[1], J. A. NOAH[1], D. PURUSHOTHAMAN[4], S. SANCHEZ-ALONSO[2], M. TIEDE[1], J. HIRSCH[3];
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Abstract: Background: Functional near-infrared spectroscopy (fNIRS) enables portable cortical hemodynamic measurement in naturalistic and clinical settings, but spatial resolution is limited to about 3 cm. Integration with functional MRI (fMRI) is hindered by coregistration relying on scalp landmarks (inion, nasion, preauricular points, and Cz) often occluded by the optode cap, causing spatial blur and inter-subject misalignment in group analyses.Objective: We developed a

surface-based registration and hyper-resolution framework that aligns concurrent fNIRS and fMRI without landmarks and improves group-level spatial resolution of fNIRS activation maps.
Methods: Adults performed finger-tapping during fNIRS (Shimadzu) and fMRI. fNIRS underwent global component removal, filtering, and GLM estimation; fMRI volumes were analyzed with GLMs in MNE. Each participant's cap and head were scanned with a Structure Sensor (Structure.IO); optodes localized in MeshLab (Cignoni et al., 2008). A T1-derived head model was generated with brain2print (Rorden et al., 2025). Exposed facial surfaces (excluding cap and hair) from both meshes were aligned via the iterative closest point (ICP; Besl & McKay, 1992) into fMRI space. fNIRS GLM maps were projected onto MNI cortical surfaces; group t-tests and cluster statistics followed. Cross-subject anatomical variability in optode placement and cortical folding enabled hyper-resolution group maps beyond inter-optode spacing.
Results: ICP registration aligned independently acquired models: Structure Sensor face mesh (red), T1-derived mesh (blue), and optode locations (green) in fMRI space showed consistent facial geometry and stable optode positioning across modalities.
Conclusions: Surface-based ICP enables precise fNIRS-fMRI colocalization without occluded landmarks. Hyper-resolution analysis leverages inter-subject anatomical diversity to sharpen population-level fNIRS maps while validating optical imaging against concurrent fMRI.



Red: the face from fNIRS model registered into fMRI model, **blue:** the face from fMRI model, **green:** the locations of optodes. **Activity:** upper row: group analysis for fMRI. Lower row: group analysis for fNIRS.

Disclosures: X. Zhang: None. **J.A. Noah:** None. **D. Purushothaman:** None. **S. Sanchez-Alonso:** None. **M. Tiede:** None. **J. Hirsch:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.14/KK33

Topic: J.04. Physiological Methods

Support: Brown Subaward 00002443 / NIH Grant

Title: Cortex-wide all-optical electrophysiology in behaving mice

Authors: *Y.-C. HUANG[1], Y. QI[1], P. PARK[1], X. WU[1], S. NARAYAN[2], B. TASIC[2], A. E. COHEN[1];
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Abstract: To understand neural computation, one would like to record and stimulate the electrical activity of large ensembles of neurons, across scales from individual microcircuits to brain-wide activity. We developed (1) transgenic mice which conditionally express a red-shifted voltage indicator and, optionally, a spectrally orthogonal blue-excited channelrhodopsin; (2) optical instrumentation for high-speed and wide-area spatially patterned optogenetic stimulation and structured illumination voltage imaging; and (3) protocols and data analysis algorithms for mapping information flow across the cortex and between cortical cell types.Using this system, we delivered targeted optogenetic stimuli to defined loci and cell types across the dorsal cortex and mapped the patterns of evoked activity. These experiments revealed characteristic propagation motifs which reflect hierarchical information processing in cortex. We then compared activity patterns from whisker stimulation and from focal optogenetic stimuli delivered to the whisker barrel cortex. The mice, instrumentation, and methods are a broadly useful resource for exploring excitability and synaptic transmission across cell types and brain regions. As a high-bandwidth bidirectional brain-computer interface, these tools could also guide development of other brain-interfacing technologies.

Disclosures: Y. Huang: None. **Y. Qi:** None. **P. Park:** None. **X. Wu:** None. **S. Narayan:** None. **B. Tasic:** None. **A.E. Cohen:** A. Employment/Salary (full or part-time):; Luminos LLC. F. Consulting Fees (e.g., advisory boards); Quiver Biosciences, Exin Therapeutics.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.15/KK34

Topic: J.04. Physiological Methods

Support: R01MH133066
R01NS130361
R01MH126351
1K99EY035752

Title: Two-photon Spectral Classification for Multicolor Imaging of Many Simultaneous Neural Subpopulations In Vivo

Authors: *G. R. HELLER[1], T. OSAKI[2], S. K. ÄHRLUND-RICHTER[1], S. SOOTER[4], K. R. JENKS[3], M. SUR[5];
[1]MIT, Cambridge, MA; [2]Picower Inst. for learning and memory, MIT, Boston, MA; [3]Picower Inst., MIT, Cambridge, MA; [4]Univ. of Arkansas Fayetteville, Fayetteville, AR; [5]Dept. of Brain and Cognitive Sci., MIT, Dept. of Brain and Cognitive Sci., Cambridge, MA

Abstract: We present and characterize Excitation-Emission Spectral Unmixing for two-photon microscopy (EESU-2P), a dual-domain unmixing framework that leverages both excitation-dependent and emission-dependent spectra to improve fluorophore separability for two-photon imaging in vivo. We first demonstrate the separability of three spectrally overlapping red fluorophores: TdTomato, mCherry, and mNeptune. We utilize this fluorophore set for two example use cases: classification and recording of four transcriptomic neuronal classes (PV, SST, VIP and Other), and of four excitatory projection populations (ACC, RSP, AUD, and Other). We find that ACC projecting neurons in V1 encode less visual information than the other populations. We also utilize these fluorophores to establish practical limits for spectral classification in vivo: 30-degree angular separation as a practical bound for separability, and 60-degree angular separation for identifying dual-labeled cells. We demonstrate that utilizing multiple asynchronous excitations at different wavelengths improves separability relative to emission-based unmixing alone. We identify important considerations for applying the technique, including XY alignment, compensation for wavelength-dependent axial focal shift, and the inclusion of both spectral GCaMP states during fluorophore selection. While our demonstrations are conducted in mouse cortex, the technique is versatile and directly applicable to other samples (cell culture, slice, organoids, Drosophila, C. elegans, etc.) without special optical integration or hardware requirements. The two primary limitations are the selective expression of the fluorophores and computational tool availability. To address the latter, we provide a suite of software tools (UNICORN) to facilitate the three steps of the technique: 1. fluorophore and system selection, 2. system verification, and 3. processing, classification, and QC. Together, these results establish EESU-2P as a practical and broadly deployable approach for multicolor spectral classification.

Disclosures: G.R. Heller: None. **T. Osaki:** None. **S.K. Ährlund-Richter:** None. **S. Sooter:** None. **K.R. Jenks:** None. **M. Sur:** None.

Poster

PSTR116: Optical Methods II

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR116.16/KK35

Topic: J.04. Physiological Methods

Support: R21NS143157
P30DA048742

Title: Cerebellum-wide cellular imaging in freely behaving animals

Authors: I. OLADEPO[1], K. SAXENA[2], A. K. NIETZ[3], A. CHERKKIL[4], M. HJORT[3], J. HU[7], R. PETERS[5], R. CARTER[3], M. L. STRENG[6], T. J. EBNER[3], *S. B. KODANDARAMAIAH[8]; [1]Mechanical Engin., Univ. of Minnesota, Twin Cities, Saint Paul, MN; [2]Mechanical Engin., [3]Neurosci., [4]MECHANICAL ENGINEERING, [6]Dept. of Neurosci., [5]Univ. of Minnesota, Minneapolis, MN; [7]Mechanical Engin., The Univ. of Minnesota, Twin Cities, Minneapolis, MN; [8]Univ. Of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Over the past decade, head-mounted miniscopes have transformed neuroscience. Yet we have a limited understanding of how cerebellar dynamics coordinate motor and non-motor functions particularly in freely behaving animals. Existing recording methods cannot capture cellular-resolution population activity across multiple folia in freely moving animals, the conditions under which their full behavioral repertoire is expressed. To address this challenge, we developed the CerebellumCAM. By integrating a low-light CMOS sensor and off-the-shelf optics with a transparent polymer window implant, the system captures a 17 mm² area of the cerebellar cortex at 8.76 µm full-pitch resolution. The microscope is easy to attach and remove via a magnetic head-docking mechanism, and it records during long-term free behavior with minimal motion or light artifacts.We tested the miniaturized microscope in freely behaving mice during an open-field task with cued reward delivery, while imaging Ca2+ activity in 100s of Purkinje cells across four cerebellar folia. The mice move naturally, grooming and rearing with the scope attached. This platform enables studying cerebellar computations across a full range of natural behaviors, improving our understanding of how the cerebellum contributes to both motor and non-motor processing.

Disclosures: I. Oladepo: None. **K. Saxena:** None. **A.K. Nietz:** None. **A. Cherkkil:** None. **M. Hjort:** None. **J. Hu:** None. **R. Peters:** None. **R. Carter:** None. **M.L. Streng:** None. **T.J. Ebner:** None. **S.B. Kodandaramaiah:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Objective Biotechnology Inc.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.01/KK36

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

Title: Generating Self-Authenticating Computational Operators for Governance of Metacognitive Human-AI Co-Creation Journeys

Authors: *P. PENNEFATHER;
Univ. of Toronto, Toronto, ON, Canada

Abstract: Humans-AI interactions generate co-created meta-informatic (MI) cognitive artifacts: digital objects such recordings, demonstrations, and disclosures that act as creative-work markers and guide metacognitive as monitoring of work in service/craft delivery, research/implementation, and other self-regulated professional domains. These MI cognitive artifacts function as syntactic artifact computational operators whose information structure (e.g., wording, syntax, metadata), transformed by regime-specific interpretive rules, serves as decisive input to technology-regime decision processes and shapes how chains of thought emerge.
A method is proposed for empirically characterizing Operational Human-AI Artifact Authenticity Co-Creation (HAACCs) chains of thought, in which structured representations of cognitive artifact latent space vectors are generated, temporally aligned, and uniquely identified using public-key signatures as accountable explicit encodings and discursive accounts of human-AI co-creation journeys.
In some embodiment, these vectors include descriptive fields encoding qualitative evaluations of self and AI contributions, together with answers to discursive queries regarding characterization, categorization, confirmation, and continuity of thoughts and their associations.
he method enables decision-support, record-keeping, and rights-governance systems to assert, validate, and constrain allocation of rights and interests across human-AI co-creation trajectories, thereby preserving human agency and ownership of chains of thought created with AI assistance.
The model encodes information artifacts using an informatic-holograph framework that represents normalized superposition mixtures of stance and meaning association in a latent governance manifold (MxS LSM). Within this geometric space, phenomenal qualia and their evoked meaning-manifolds are treated as empirically attributed meaning interfaces that transform between a higher-dimensional semiotic/ syntactic categorization space and a lower-dimensional teleodynamic/ morphodynamic configuration manifold.
Holograph-like evocation of qualia defines trajectories on the governance manifold that configure how analogous situational episodes acquire qualitatively tacit and quantitatively explicit media-stance meanings for specific persons over time.
This cognitive-artifact model is designed to interact faithfully with the plurality of stance-meaning configurations instantiated in humans by an evolved excitation/inhibition brain medium that supports plastic forms of consciousness and qualified chains of thought.

Disclosures: P. Pennefather: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Owner of gDial Inc and associated patents for commecializing this computation system, President gDial Inc.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.02/KK37

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

Support: NSF PHY-2309135
Gordon and Betty Moore Foundation Grant No. 2919.02
Shanghai Pilot Program for Basic Research - FuDan University 21TQ1400100 (22TQ019)
the Foundation of the Shanghai Municipal Education Commission No. 24RGZNA01
Simons Collaboration on the Global Brain
the Vannevar Bush Faculty Fellowship Program of the U.S. Department of Defense

Title: A geometric and dynamical theory of latent computations in biological neural networks

Authors: *F. DINC[1], M. BLANCO-POZO[2], D. KLINDT[5], F. ACOSTA[6], Y. JIANG[3], C. SYLBER[2], M. EBRAHIMI[7], A. SHAI[4], H. TANAKA[8], P. YUAN[9], N. MIOLANE[1], M. J. SCHNITZER[10];
[1]UC Santa Barbara, Santa Barbara, CA; [3]Electrical Engin., [2]Stanford Univ., Stanford, CA; [4]Stanford Univ., Palo Alto, CA; [5]Cold Spring Harbor, Cold Spring Harbor, NY; [6]Geometric Intelligence Lab, UC Santa Barbara, Goleta, CA; [7]Electrical Engin., Synchron, BROOKLYN, NY; [8]NTT Res. at Harvard, Cambridge, MA; [9]Fudan Univ., Shanghai, China; [10]Depts. Biol. & Applied Physics, Stanford University, HHMI, Stanford, CA

Abstract: Many studies have identified low-dimensional sets of behavioral variables encoded within large-scale neural activity patterns. However, dimensionality reduction analyses alone cannot yield causal explanations for how networks stably implement computations that are resilient to the substantial variability of single neuron dynamics. Further, existing methods for dimensionality reduction often rely on simplifying assumptions about network structure that limit their applicability and explanatory power. To provide a theoretical framework describing the dynamics of low-dimensional computation in high-dimensional neural networks, here we introduce the concept of latent processing units (LPUs), which are architecture-agnostic computational elements operating within biological neural circuitry. Six theorems governing coding and computation by LPUs collectively provide explanations for a range of common biological findings: low-dimensional sets of coding variables can generate high-dimensional neural dynamics; many neurons have activity patterns that represent behaviorally relevant variables but exert little influence on downstream circuits; linear readouts of neural population activity commonly allow near-optimal decoding of behaviorally relevant variables; drift in neural representations are often substantial even while network computations remain intact. Overall, our treatment of LPUs enacted in network dynamics unifies the geometric and dynamical views of neural computation under a joint framework and provides systems neuroscience with a causal account of how the brain executes reliable computations.

Disclosures: F. Dinc: None. **M. Blanco-Pozo:** None. **D. Klindt:** None. **F. Acosta:** None. **Y. Jiang:** None. **C. Sylber:** None. **M. Ebrahimi:** None. **A. Shai:** None. **H. Tanaka:** None. **P. Yuan:** None. **N. Miolane:** None. **M.J. Schnitzer:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

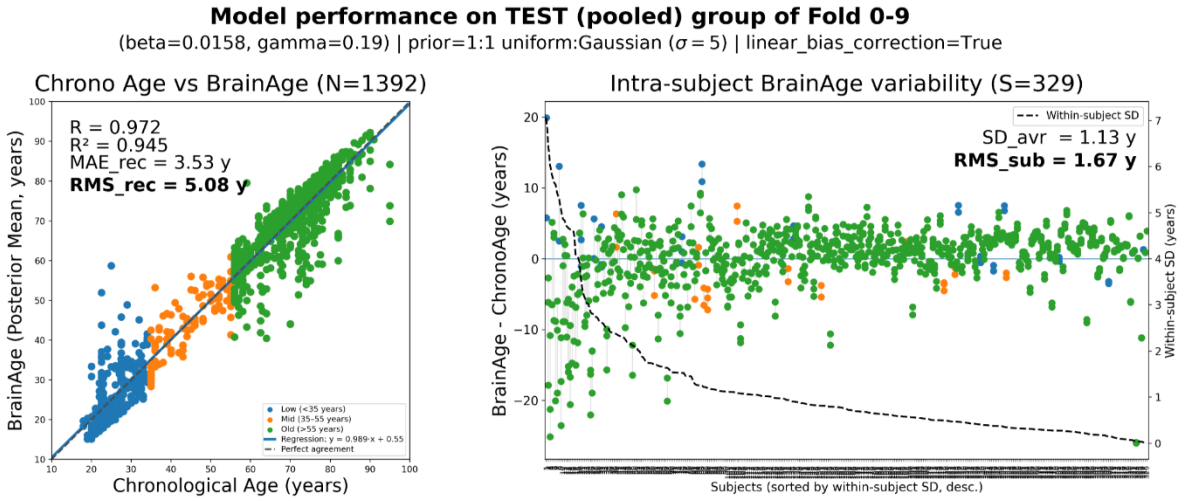
Program #/Poster #: PSTR117.03/KK38

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

Title: When neuroscience is data-limited, Bayesian generative inference outperforms neural networks

Authors: *J. DREO, B. MOHORCIC;
BrainTrip, Naxxar, Malta

Abstract: Neural networks have become increasingly used in neuroscience. However, most neuroscience research is heavily data-constrained and often falls short of the big-data ideal typical of machine learning. This limitation is particularly acute in EEG research, where datasets typically have up to 50 subjects, are noisy, and highly multidimensional. Furthermore, EEG biomarkers are usually only weakly or moderately correlated with some variable of interest (say a mental state). We compared a neural-network approach (MLP) with a Bayesian generative inference (BGI) framework for regressing an easily measurable variable from EEG data- namely, subjects' chronological ages. The dataset had 1392 EEG recordings, which were distilled into about 1000 biomarkers encompassing spectral, spatial, and signal-complexity features of each subject’s EEG. Instead of directly mapping all biomarkers to age, the BGI framework first models the age-conditional distribution of each biomarker, accounting for age-dependent location, variance, and skewness. Each biomarker observation was then inverted into probabilistic age evidence. Evidence across biomarkers was integrated using covariance-aware weighting to ameliorate redundancy among correlated biomarker features. Model performance was evaluated across pooled test folds and compared with a multilayer neural-network (MLP). The neural-network model achieved a MAE=4.7 years, and RMS error=6.7 years. In contrast, the BGI framework achieved MAE=3.5 years, and RMS error=5.1 years. Test-retest stability also improved: among 329 subjects with repeated recordings, within-subject brain age variability decreased from 2.2 years for the neural network to 1.7 years for BGI. Our results indicate that, in data-limited yet feature-rich neuroscience, explicitly modeling biomarker distributions and dependence structures can greatly outperform direct “black-box” MLP regression. The BGI framework provides a data-efficient and interpretable alternative for generating robust predictions from noisy, high-dimensional neural biomarkers.



Disclosures: J. Dreo: A. Employment/Salary (full or part-time):; BrainTrip. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainTrip. **B. Mohorcic:** A. Employment/Salary (full or part-time):; BrainTrip.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.04/KK39

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

Support: NSF CAREER award 2340338
Howard Hughes Medical Institute

Title: Behavior-dLDS: A decomposed linear dynamical systems model for neural activity partially constrained by behavior

Authors: *E. YEZERETS[1,2,3,4], E. YANG[5], M. B. AHRENS[6], A. CHARLES[1,2,3,4]; [2]Biomed. Engin., [3]Kavli Neurosci. Discovery Inst., [4]Ctr. for Imaging Sci., [1]Johns Hopkins Univ., Baltimore, MD; [5]Biol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Janelia Res. Campus / HHMI, Ashburn, VA

Abstract: Brain-wide recordings of large-scale networks of neurons now provide an unprecedented view into how the brain drives behavior. However, brain activity contains both information directly related to behavior as well as the potential for many internal computations. Moreover, observable behavior is executed not only by the brain, but also by the spinal cord and peripheral nervous system. Behavior is a coarse-grained product of neural activity, and we thus take the view that it can be best represented by lower-dimensional latent neural dynamics.

Capturing this indirect relationship while disambiguating behavior-generating networks from internal computations running in parallel requires new modeling approaches that can embody the parallel and distributed nature of large-scale neural populations. We thus present behavior-decomposed linear dynamical systems (b-dLDS) to disentangle simultaneously recorded subsystems and identify how the latent neural subsystems relate to behavior. We assess the robustness of the model to initialization and hyperparameter settings to confirm that its outputs are reliably interpretable in terms of mapping the model to the behavior. We demonstrate the ability of b-dLDS to decouple behavioral vs. internal computations on controlled, simulated data, showing improvements over a state-of-the-art model that uses behavior to supervise all dynamics based on behavior. We show that b-dLDS can recover which system or systems were used to generate simulated "behavior" out of a larger set of systems used to generate the overall "neural" state. We also demonstrate b-dLDS's interpretability benefits on a task-driven RNN dataset featuring a nonlinear relationship between behavior and activations. We compare b-dLDS to b-dLDS-x, a version of b-dLDS that maps the latent states, rather than the dynamics coefficients, directly to the behavior, and show that this forces a less interpretable and dense mapping in b-dLDS-x in the case of nonlinearity. We then show that b-dLDS can further scale up to tens of thousands of neurons by applying our model to a large-scale recording of a zebrafish hindbrain during the complex positional homeostasis behavior. b-dLDS can reconstruct neural and behavior data, integrate trial type information to learn latent neural dynamics that parse the session into trials, and can separate strongly- vs. weakly- behavior-related dynamics, which show differences in their utilization over time. Moreover, b-dLDS highlights asymmetry in behavior-related, hindbrain-wide dynamic connectivity networks that may offer evidence of zebrafish hindbrain lateralization.

Disclosures: E. Yezerets: None. **E. Yang:** None. **M.B. Ahrens:** None. **A. Charles:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.05/KK40

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

Support: DOE/NSF CRCNS
ASCR Enabling Manufacturing

Title: Competitive Sparse Coding Models Optimized with Equilibrium Propagation for Visualizing and Predicting Functional Multi-Channel LFP Ensembles in the Rodent Visual Cortex

Authors: *N. G. BRUNS, G. T. KENYON;
CAI-3, Los Alamos Natl. Lab., Los Alamos, NM

Abstract: Existing methods to interpret vast neuroscience datasets often fail to adequately scale to the spatiotemporal resolution necessary to understand how information is encoded across large neuronal ensembles. As neuroscientific discovery increasingly shifts towards reliance on miniaturized recording tools capable of recording vast swathes of the brain with microscopic precision across thousands of channels simultaneously, the methods available to interpret these datasets in their entirety are insufficient; reliant on dimensionality reduction that discards fine spatiotemporal structure, or biologically implausible and uninterpretable deep neural nets or transformers.

Here, we present a neuromorphic method well suited for extracting & interpreting fine multiscale features from vast datasets, and how it can be implemented to decode latent sensory information using the Allen Brain Observatory Neuropixels Visual Coding dataset.

We demonstrate how this approach can factor raw local field potentials (LFPs) recorded from the rodent primary visual cortex (VISp) into interpretable features (Fig. 1, bottom left) using a locally-competitive algorithm (LCA) implementing sparse coding. These features are heavily suggestive to be directly representative of functional ensembles of activity in VISp and thus are likely to be encoding visual sensory precepts. We next demonstrate how these LFP features can be further improved with the addition of biologically plausible equilibrium propagation (EP) to optimize for LFP reconstruction & stimulus inference. With this method, we are able to map LFP features directly to the visual receptive fields (RFs) that they encode (Fig. 1, top left). A subset of these mapped RFs and corresponding LFP features can be seen in the right brace of figure 1.

In figure 2, we show how solving the inverse problem is possible by using the RFs as starting features to sparse code the stimuli, improving them with EP to arrive at features which reconstruct stimuli while inferring LFP activity.

[1] Rozell, Neural Comp. 2008.[2] Scellier & Bengio, Front. Comp. Neurosci., 2017

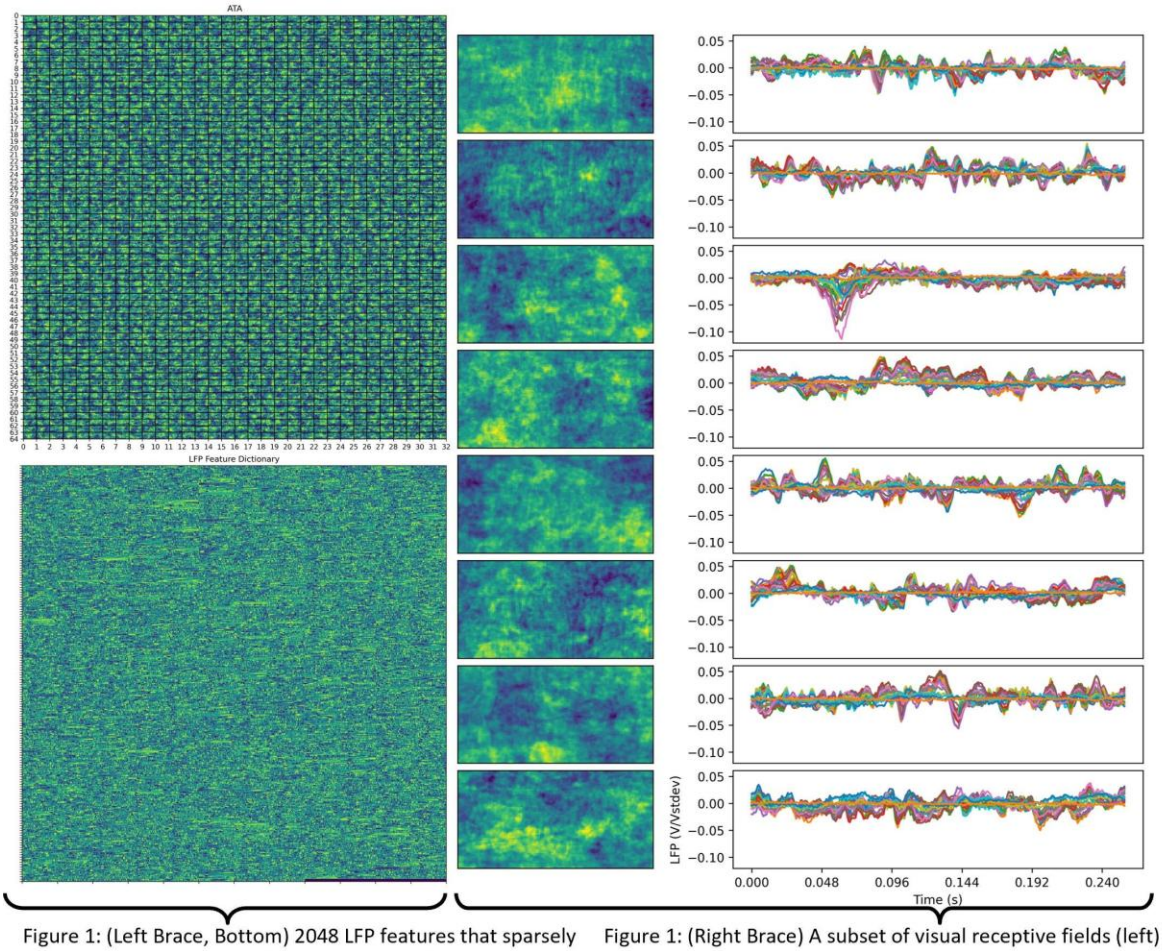


Figure 1: (Left Brace, Bottom) 2048 LFP features that sparsely factor VISp LFP activity. (Left Brace, Top) 2048 visual receptive fields which map directly to a corresponding LFP feature.

Figure 1: (Right Brace) A subset of visual receptive fields (left) and their corresponding voltage traces (right)

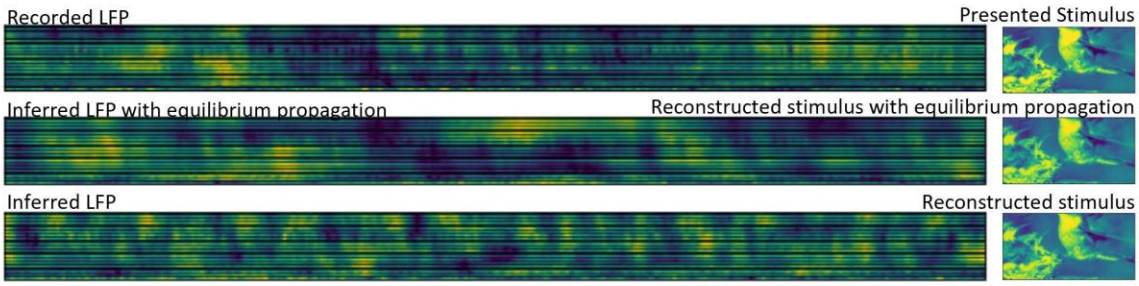


Figure 2: Recorded LFP and originally presented stimulus (top row). Inferred LFP response and sparsely reconstructed stimulus using equilibrium propagation to improve features (middle row). Inferred naive LFP activity and reconstructed stimulus without EP.

Disclosures: N.G. Bruns: None. **G.T. Kenyon:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.06/KK41

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

Title: Brain semantic mapping across multiple supervision sources: human behavioral features versus language-model embedding in fMRI

Authors: *D.-H. SIM[1], D.-H. JEONG[1,2];
[1]Healthcare and Artificial Intelligence, The Catholic Univ. of Korea, Bucheon-si, Korea, Republic of; [2]Artificial Intelligence, The Catholic Univ. of Korea, Buchoen, Korea, Republic of

Abstract: Decoding semantic representations from fMRI requires a supervisory signal, but the sources of semantic supervision have not been systematically compared. Therefore, it remains unclear whether decoded representations reflect intrinsic neural geometry or the structure of a particular embedding space. We investigated the capacity of each supervision source to recover neural geometry and validated the recovered structure using representational similarity analysis (RSA) and functional connectivity (FC) analysis. Using fMRI responses to 672 words from 11 participants in a publicly available fMRI concept representation dataset, we developed a subject-invariant contrastive multilayer perceptron (C-MLP) combining an InfoNCE objective with a semantic alignment loss. We compared four supervision sources: human behavioral ratings and embeddings from three large language models (BERT, Electra, and GPT-2). C-MLP achieved robust decoding (2-vs-2 accuracy: word-split 0.772; subject-split 0.706), exceeding ridge regression (0.662/0.528) and a standard MLP (0.607/0.509). RSA between fMRI and embedding representational dissimilarity matrices (RDMs) revealed that human behavioral ratings best recovered neural geometry ($r=0.23$), whereas language model embeddings showed substantially weaker alignment ($r=0.03$-0.12; all $p<0.05$). The seven canonical resting-state networks also corresponded to semantically defined word clusters ($k=7$) above chance (normalized mutual information > 0.18, $p<0.05$) and were consistent with established functional organization: visual networks preferred perceptual-attribute words and the default mode network preferred social-role words. The convergence of RSA and network-level evidence indicates that the recovered geometry reflects neural organization. Among the supervision sources tested, human behavioral ratings most faithfully recovered neural geometry, indicating that the geometry of the supervising semantic space governs neural alignment.

Disclosures: D. Sim: None. **D. Jeong:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.07/KK42

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

Title: Dynamic optimal temporal resolution of visual coding reflects evolving population response geometry

Authors: *T. SAMIEI[1], S. LOKRAY[2], H. AHMED[3], E. NOZARI[4];
[1]Univ. of California, Riverside, CA; [2]Boston Univ., Saratoga, CA; [3]UCR, Riverside, CA;
[4]Mechanical Engin., Univ. of California, Riverside, Riverside, CA

Abstract: Understanding neural coding requires determining not only which populations encode information, but also the temporal scale at which this information is structured. Most analyses use a fixed bin size across the trial, implicitly assuming the same resolution before, during, and after stimulus processing. Here, we asked whether the optimal temporal resolution of visual coding is dynamic, and which population-level statistics shape this changing scale.Using an adaptive split-merge procedure in Allen Neuropixels visual recordings, we estimated average optimal bin size over time across LGd, VISp, and higher visual areas. Counter to the intuition that peak information should require finer temporal precision, average merged-bin length increased after stimulus onset, remained elevated during the response epoch, and decreased later. This increase was consistent across visual regions and revealed hierarchical organization across the visual pathway.We then examined independent factors that could explain this time-varying resolution. Stimulus decodability rose approximately 40-50 ms after stimulus onset, defining an information-rich epoch lasting about 100 ms. Total entropy increased during the same epoch and returned toward baseline, indicating transient expansion of response variability. Signal correlations, measured as cosine similarity between class-averaged population vectors across time, increased during information arrival and decayed with temporal distance, showing that neighboring time bins became more coherent. In contrast, noise correlations followed an opposing profile, decreasing when signal correlations and decodability increased. This divergence suggests that temporal averaging becomes beneficial when coherent signal rises relative to noise, explaining why optimal bin size expands near peak information and remains mesoscale afterward.Finally, we modeled neural activity as a dynamical system driven by previous neural state and visual stimulus input. Although nonlinear fusion outperformed linear fusion overall, their difference was minimized near peak information, indicating that the response was most linearly accessible when stimulus information was strongest.Together, these results show that optimal temporal resolution is an evolving property of visual coding, not a fixed preprocessing choice. Entropy, signal-noise correlations, and linear accessibility provide a mechanistic explanation for the split-merge trajectory: optimal bin size expands when stimulus-driven activity becomes more variable, temporally coherent, less noise-dominated, and more linearly accessible.

Disclosures: T. samiei: None. **S. Lokray:** None. **H. Ahmed:** None. **E. Nozari:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.08/KK43

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

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Title: Uncovering shared, brain-wide latent dynamics in larval zebrafish

Authors: *A. AGARWAL[1,3], A. ZYLBERTAL[4], F. ZHU[6], I. H. BIANCO[5], M. T. KAUFMAN[8], C. PANDARINATH[9,2,7];
[2]Ctr. for Machine Learning, [1]Georgia Inst. of Technol., Atlanta, GA; [3]Wallace H. Coulter Dept. of Biomed. Engin., Emory Univ. and Georgia Inst. of Technol., Atlanta, GA; [4]Neuroscience, Physiol. & Pharmacol., [5]Univ. Col. London, London, United Kingdom; [6]Neurosci. Grad. Program, [7]Dept. of Neurosurg., Emory Univ., Atlanta, GA; [8]Organismal Biol. and Anat., Univ. of Chicago, Chicago, IL; [9]Biomed. Engin., Emory Univ. and GA Tech., Decatur, GA

Abstract: Modern neuroscience methods, in particular functional calcium imaging, enable access to the activity of tens of thousands of neurons. However, extracting the underlying dynamics governing distributed population activity remains challenging, especially across animals or recording sessions. A recent deep learning method, Free-RADICaL (FR; Agarwal et al SfN 2023) infers neural population dynamics at high temporal resolution even at slow imaging frame rates (<5 Hz). FR incorporates a generative model of calcium indicator fluorescence and a novel optimization objective that separates neural dynamics from indicator dynamics, enabling direct application to fluorescence signals. We previously showed that applying FR to 2-photon imaging data from motor and visual cortices yields better estimates of single trial activity as compared to conventional approaches. Here, we show that FR can be used to study the shared latent dynamics of whole-brain activity across multiple individuals. We applied FR to whole-brain, cellular-resolution neural activity data from 11 larval zebrafish acquired using light sheet microscopy at 5 volumes per second. Fish were exposed to prey-like and whole-field motion visual stimuli, as well as acoustic tones and mild electric shocks, while their sensorimotor behavior was monitored. A shared latent representation, where dynamic factors captured similar distributed patterns of neural activity across individuals, emerged unforced by training the model jointly with all fish. Representational Similarity Analysis revealed that the mean latent representation of sensorimotor events gradually became more similar across fish during model training, despite the model being blind to stimuli and behavior. Remarkably, although FR was trained without information about neuronal locations or neuron-to-neuron correspondence across fish, the learnt factors exhibited consistent anatomical organization: the spatial distributions of their loadings onto neurons were similar across animals. The shared representation was abolished when the model was trained on individual fish sequentially. This demonstrates that FR not only

denoises and recovers high-resolution single-session dynamics directly from fluorescence, but also aligns brain-wide activity across fish into a common latent space, where shared factors capture consistent stimulus and behavior-related structure across animals. This provides a powerful framework for identifying conserved patterns of distributed neural activity across animals.

Disclosures: A. Agarwal: None. **A. Zylbertal:** None. **F. Zhu:** None. **I.H. Bianco:** None. **M.T. Kaufman:** None. **C. Pandarinath:** A. Employment/Salary (full or part-time):; Research Scientist, Meta.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.09/KK44

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

Title: Sparse Symbolic Regression and Retinal Circuit Model Yields Computational Principles of a Vertebrate Escape Circuit in Zebrafish

Authors: *A. DEEN, A. HEIN, L. GALLART, Sr;
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Abstract: Escape responses to visual threats represent one of the most conserved sensorimotor transformations in vertebrate neurobiology. In naturalistic settings, threats frequently enter the visual field of a single eye, and prior work in zebrafish (Danio rerio) has established that selection among multiple monocular threats is initially performed in the retina. To characterize this sensorimotor transformation, we developed a two-component computational framework linking behavioral dynamics to retinal circuit mechanisms. Our first step was to identify which features of an approaching threat are most relevant to escape behavior by applying Sparse Identification of Nonlinear Dynamics (SINDy), a symbolic regression framework, to behavioral data. The data was collected via automated tracking of zebrafish pairs exposed to a closed-loop paradigm in which looming dots actively pursue the zebrafish. Per-frame measurements of perceived angular size, stimulus position, and looming dynamics were extracted from the tracking data as candidate visual input features; changes in swimming speed and angular velocity served as motor outputs to be predicted. Preliminary SINDy results reveal nonlinear interactions among inputs, with coefficient weights reflecting the relative dominance of each input. Specifically, turning dynamics were most strongly governed by retinal stimulus size, while speed dynamics were shaped by a combination of external visual inputs and the zebrafish's own motion. To understand how the retina processes and selects among multiple stimuli using these behaviorally relevant features, we constructed a biologically grounded retinal circuit model formalized as an Ordinary Differential Equation (ODE) system. In this circuit, bipolar cells relay visual input, amacrine cells mediate lateral inhibition to implement threat selection, and ganglion

cells produce output passed to downstream circuits. The dominant features identified by SINDy serve as inputs to this circuit, under the assumption that the features most predictive of escape behavior are the same ones the retina operates on during threat selection. Taken together, this framework combines behavioral modeling with a biologically constrained retinal circuit model to reveal the visual features and computations underlying retinal selection.

Disclosures: A. Deen: None. **A. Hein:** None. **L. Gallart:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.11/KK46

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

Title: Brain Network Dynamics from EEG: A Coupled-Control Model, a Criticality Replication, and an Interactive Source-Space Viewer

Authors: *M. HOUSE[1,2], P. GOODYEAR[3];
[1]Ethical Emerging Technologies Lab., Montclair, NJ; [2]IMAFh Res., Camden, DE; [3]IMAFh Res., CAMDEN, DE

Abstract: Cognitive flexibility (CF) and emotion regulation (ER) are typically treated as separable faculties, yet they share sub-processes, attentional shifting, inhibitory control, reappraisal, emotional awareness, set switching, and distress tolerance that influence one another continuously. We test whether CF and ER are better described as a single coupled control system than as independent modules. The six sub-processes are modeled as nodes of a continuous-time-inspired recurrent neural network (RNN) whose learned recurrent weight matrix encodes directed, signed effective connectivity; per-node time constants, a spectral-radius stability constraint, and L1 sparsity yield bounded, interpretable dynamics. We validated the framework in three stages. (1) On synthetic data generated from connectivity unknown to the model, it recovered directed couplings faithfully ($r \approx 0.91$; sign accuracy 1.0) across noise, coupling-strength, and sample-size regimes. (2) Against an uncoupled (diagonal) RNN and a linear vector-autoregressive model, the coupled model achieved superior held-out multi-step forecasting—direct evidence that CF and ER are not separable modules. (3) On resting-state EEG from the MPI Leipzig Mind-Brain-Body (LEMON) dataset (~200 adults; 62-channel; eyes-open and eyes-closed), the six nodes were mapped onto band-power features in sliding windows; learned connectivity converged with an independent Granger-causality estimate ($r \approx 0.53$) under subject-level cross-validation, while exploratory symptom-load comparisons showed only weak group differences. To link node-level coupling to circuit-level excitation-inhibition (E/I), we reimplemented the critical-oscillations (CROS) model and a criticality/E-I metric suite (long-range temporal correlations, branching ratio, functional E/I), reproducing emergent ~10 Hz oscillations and the passage of functional E/I through unity across the critical transition. An

interactive, source-localized viewer animates cortical connectivity with per-region statistics. By coupling interpretable models to openly available EEG, this work recasts CF and ER as an integrated, bidirectional control system and supplies reproducible, falsifiable tools for probing how regulatory sub-processes and E/I balance constrain brain dynamics.

Disclosures: M. House: None. **P. Goodyear:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.12/KK47

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

Support: NSF Graduate Research Fellowship DGE-2444107
NIH R01AG092459

Title: Multimodal integration and trajectory generation for uncovering latent phenotypic factors

Authors: *R. IRITANI[1], N. HAYES[1], V. UMASHANKAR[2], Y. CAO[3], C. C. KACZOROWSKI[3], A. DRAELOS[1];
[1]Biomed. Engin., [2]Computat. Med. and Bioinformatics, [3]Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: High-dimensional biological data can contain nonlinear patterns distributed across multiple data types and missed by linear, single-modality models. Understanding how diverse features impact cognition requires integration across datasets, such as transcriptomic data from different brain regions. We developed a multi-modal Variational Autoencoder (VAE) (Fig.1A) to identify latent features that collectively influence phenotype. We used a Conditional-Gaussian Mixture VAE to shape a latent space aligned with cognitive outcome (Fig.1B), creating a gradient from low to high cognitive resilience. We combined this with a Mixture-of-Experts framework to disentangle shared and private features between modalities influencing cognition. We applied our model to hippocampus and prefrontal cortex snRNA-seq data from AD-BXD mice who exhibit varying levels of resilience to cognitive decline. We found that our model can produce a latent space aligned with resilience while preserving intra- and cross-modal reconstruction fidelity. Latent dimensions exhibited both divergent and aligned cognitive profiles across regions, suggesting that the model learned to separate genetic features associated with cognition into region-specific and shared elements. We can traverse such resilience-aligned latent spaces to identify novel sets of features covarying with phenotype. However, these spaces are often too complex for linear methods. We previously developed an algorithm to generate trajectories bound to data-dense regions. Here we extend this method to produce local resilience distributions with lower variance via generation of uniform samples in small hyperspheres along the trajectory. Such trajectories allowed us to identify modality-specific biological pathways

consistently over-represented in resilience-associated gene sets. These techniques could be applied to many types of neurological data to uncover combinatorial patterns relevant to phenotype.

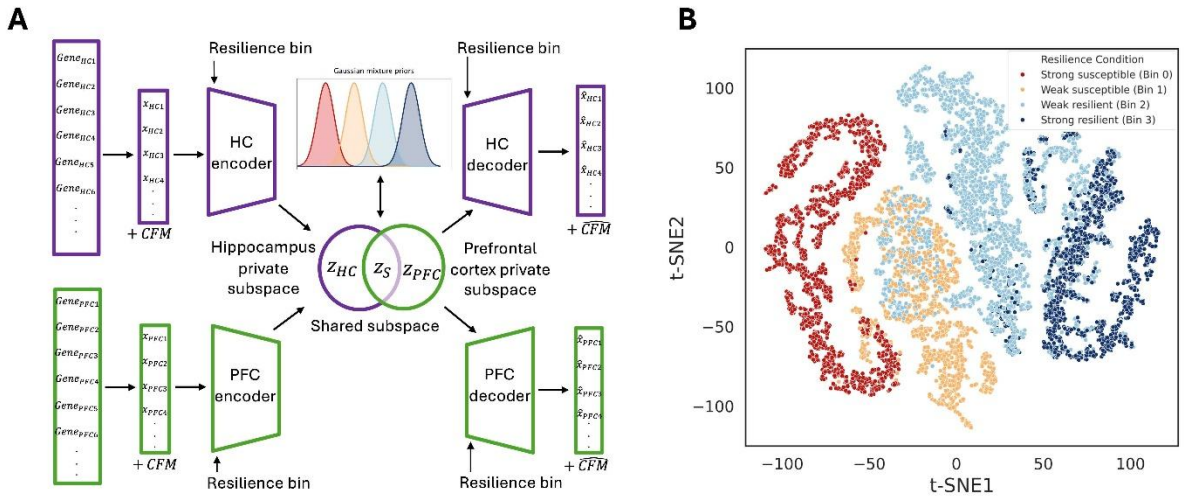


Figure 1. (A) Mixture-of-Experts VAE architecture (B) t-SNE latent space representation

Disclosures: R. Iritani: None. **N. Hayes:** None. **V. Umashankar:** None. **Y. Cao:** None. **C.C. Kaczorowski:** None. **A. Draelos:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.13/KK48

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

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National Research Foundation of Korea (NRF) RS-2023-00209473
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KAIST C2(Creative & Challenging) Project

Title: MYNE reveals stimulus- and behaviorally aligned neuronal motifs beyond rate dynamics

Authors: *G. KIM, M. EOM, Y. YOON;
KAIST, Daejeon, Korea, Republic of

Abstract: Detecting neuronal motifs from population spike trains is challenging because time-varying firing-rate covariation can generate widespread lagged co-occurrences that obscure precise spike-time statistical dependencies. We developed MYNE, a rate-conditioned, data-driven statistical test for detecting neuronal motifs beyond expected firing-rate structure. Instead of relying on analytic assumptions about stationarity or reference-lag structure, MYNE estimates time-varying spike probabilities from population activity and uses them to define a learned local baseline for expected joint events. Observed lagged co-occurrences are scored relative to this baseline, and significance is assessed using conditional surrogate spike trains that preserve single-neuron temporal structure while disrupting inter-neuronal spike-timing dependence. In synthetic data with controlled firing-rate covariation and known ground-truth motifs, MYNE more robustly recovered embedded spike-time motifs than count-based or lag-correction approaches. Applied to primate motor cortex during reaching and mouse visual cortex during drifting-grating stimulation, MYNE identified motif events aligned with movement direction and stimulus direction, respectively. These results suggest that data-driven, rate-conditioned motif testing can reveal behavior- and stimulus-aligned spike-time dependencies in time-varying population recordings.

Disclosures: G. Kim: None. **M. Eom:** None. **Y. Yoon:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

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

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KAIST Quantum+X Convergence R&D Project
KAIST C2(Creative & Challenging) Project

Title: Neuronal Identity as a Shared Organizational Principle for Neural Population Dynamics Across Individuals

Authors: *S. KIM, S. HAN, J. YOU, M. EOM, J. PARK, B. LEE, Y. YOON;
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Abstract: Understanding how neural population dynamics relate across individuals remains a fundamental challenge in systems neuroscience. Although the specific neurons recorded in each experiment differ across animals and recording sessions, many neuronal properties, including molecular identity, anatomical location, and physiological characteristics, are largely conserved within a species. We asked whether these shared biological features could provide a common organizational basis for neural population dynamics across individuals. To investigate this question, we analyzed large scale neural recordings from two distinct systems: whole brain calcium imaging with transcriptomic information in larval zebrafish and Neuropixels recordings from mouse visual cortex. We leveraged multimodal neuronal identity information to organize neural populations and examined whether such organization could reveal shared population structure across animals and recording sessions. Across both species and recording modalities, organizing neural populations according to neuronal identity enabled the identification of shared population structure in previously unseen animals without requiring explicit neuron-to-neuron correspondence. Neural representations derived from identity-based organization more accurately captured behavioral and sensory variables and preserved the temporal structure of neural activity across individuals. Importantly, these improvements were observed across multiple forms of biological information, suggesting that the benefit arises from shared neuronal identity rather than any single modality. These results support the idea that neuronal identity provides a biologically meaningful framework for relating neural population activity across individuals. More broadly, our findings suggest that molecular, anatomical, and physiological features can serve as a common reference for integrating large-scale neural recordings across animals and experimental conditions.

Disclosures: S. Kim: None. **S. Han:** None. **J. You:** None. **M. Eom:** None. **J. Park:** None. **B. Lee:** None. **Y. Yoon:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.15/KK50

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

Support: R01AA031609
R01AA027213

Title: A robust shared-state multi-neuron GLM-HMM framework for detecting internal states

Authors: *A. LAWRENCE[1], E. YEZERETS[2], P. H. JANAK[3,1], A. CHARLES[2];
[1]Neurosci., [2]Biomed. Engin., [3]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Neural systems exhibit multiple firing modes that are thought to reflect internal state and modulate the relationship between external environmental stimuli and behavior. Studies have inferred these latent states by supplementing generalized linear models (GLMs) consisting of non-Poisson behavioral observations (Ashwood et al, 2022; Calhoun et al, 2019) with traditional hidden Markov Models (HMMs). However, understanding the relationship between internal brain states and behavior requires also modeling the neural activity. Fitting multi-neuron GLM-HMMs is non-trivial due to high sparsity, collinearity, and low trial counts in neural datasets. Thus, we built a robust multi-neuron GLM-HMM framework that detects latent states from neuronal population activity while incorporating influence of time-stamped task variables and spike history. To obtain reliable model parameters, we used a modified expectation-maximization procedure. We incorporated neuron-adaptive penalization in the maximization (M) step to overcome covariate collinearity typical of time-stamped events and sparse spiking. We used a trust-region algorithm to ensure stable M-step convergence in the presence of ill-conditioned Hessians that can lead to unstable Newton-Raphson updates. We demonstrated the utility of leave-one-out cross-validation analysis for evaluating model performance on datasets with low trial counts without breaking their temporal structure. We tested our framework on publicly available electrophysiology datasets from rat medial prefrontal cortex (31 neurons, 22 trials; Peyrache et al, 2018) and monkey premotor cortex (94 neurons, 496 reaches; Perich et al, 2018), in addition to our own rat anterior insula cortex recording (96 neurons, 72 trials). Our framework yielded stable estimates of Poisson GLM-HMM coefficients across all datasets while unpenalized models were unstable. Using the trust-region algorithm, we found exponentially decreasing negative-log-likelihood with no non-finite model parameters across EM iterations. In contrast, the Newton-Raphson method resulted in exponentially increasing negative-log likelihoods and > 50% non-finite parameter estimates. The held-out trial likelihood was significantly higher when the model was trained on real as compared to shuffled data (Wilcoxon signed-rank test; $p<0.0001$), highlighting that the model was able to capture meaningful information even when trained on low trial counts. Our framework demonstrated stable convergence and revealed behaviorally relevant internal states across species and brain regions, providing a new approach to understanding brain-behavior relationships.

Disclosures: A. Lawrence: None. **E. Yezerets:** None. **P.H. Janak:** None. **A. Charles:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.16/KK51

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

Title: HAVOK modeling reveals shared neural dynamics and accurate cross-context prediction of local field potentials

Authors: *A. NECAISE[1], R. HULTMAN[2], L. FAVELA[1];
[1]Indiana Univ. Bloomington, Bloomington, IN; [2]Dept. of Mol. Physiol. and Biophysics, Univ. of Iowa, Iowa City, IA

Abstract: As large dynamic datasets become more commonplace in neuroscience, there is a great need to invest in computational strategies for interpreting these datasets. Hankel alternative view of Koopman (HAVOK) is a data-driven technique that models nonlinear timeseries as a linear system driven by intermittent forcing. HAVOK is a promising method for neural systems because it can make near-real-time predictions of signal change and identify a forcing term that captures task-relevant shifts in dynamics. Although there have been applications to electroencephalogram data, it is necessary to explore how the technique can be used to model brain activity more broadly and predict neurological outcomes. We apply HAVOK to analyze local field potentials (LFPs) recorded at 1 kHz in 7 brain regions of 7 genetically heterogenous mice. LFPs were recorded on three separate days and ranged from 152.05 to 206.07 minutes in length. Our first objective was to determine whether changes in LFP could be accurately predicted with HAVOK by testing performance on a randomly selected animal. This is an important step because HAVOK performance depends on noise and signal complexity. The model was trained using the first 100 seconds of LFP on the day 1 amygdala recording of a randomly selected mouse. The remaining 11.7 million samples were used as a test set and achieved a high level of accuracy with mean absolute error (MAE) of 0.28 and root mean square error (RMSE) of 0.68. Next, we investigated whether model accuracy would generalize across brain regions, animals, and days. This was examined by convolving the U-modes from the original model with the other signals and using data at $t = 1$ in the transformed space as initial conditions. Accuracy was remarkably consistent across contexts with an average correlation between actual and predicted signals of .83 ($SD = .08$), MAE of 0.29 ($SD = 0.04$), and RMSE of 0.57 ($SD = 0.12$). Repeated measures ANOVA revealed there were significant differences in MAE by day ($F = 6.15$, $p < .001$) and region ($F = 24.24$, $p < .0001$). Taken together, the Koopman operator model trained with 100 seconds of data in one mouse and brain region generalized to predict LFP in 7 regions, 7 animals, and 3 days of recording from $t = 1$ with total signal durations that were each 10^2 longer than the training set. This suggests that LFPs across diverse brain regions are governed by shared dynamics, such that the intermittent forcing of this system could be leveraged to identify brain state transitions.

Disclosures: A. Necaise: None. **R. Hultman:** None. **L. Favela:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.17/KK52

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

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Research Grant from HFSP (RGP003/2024)
KAIST Quantum+X Convergence R&D Project
KAIST C2(Creative & Challenging) Project

Title: Modeling neural population dynamics in the presence of stochasticity

Authors: *J. PARK, S. HAN, M. EOM, Y. YOON;
KAIST, Daejeon, Korea, Republic of

Abstract: Latent state models have emerged as a powerful framework for analyzing high-dimensional neural population activity, providing a principled way to represent coordinated neural dynamics on a low-dimensional manifold. Despite the success of this framework, accurately inferring latent trajectories remains challenging because population activity is inherently stochastic and exhibits substantial variability across repeated observations. To address this challenge, we propose a deep-learning-based method that models the stochastic nature of neural population activity. We demonstrate the effectiveness of our approach by showing that it improves behavioral decoding performance across diverse datasets, consistently outperforming standard latent state baselines and highlighting the value of modeling stochasticity as an integral component of population dynamics.

Disclosures: J. Park: None. **S. Han:** None. **M. Eom:** None. **Y. Yoon:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.18/KK53

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

Support: National Research Foundation of Korea (NRF) RS-2026-25475246
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Research Grant from HFSP (RGP003/2024)
KAIST Quantum+X Convergence R&D Project
KAIST C2(Creative & Challenging) Project

Title: Novel data driven functional parcellation with high generalizability for regional and circuit level analysis

Authors: *J. PARK, J. YOU, Y. YOON;
KAIST, Daejeon, Korea, Republic of

Abstract: Brain is a very complex organ that consists of astronomical number of neurons. Understanding brain can be done at several levels. Molecular, cellular, regional, and circuit levels. To perform scientific discovery at regional and circuit levels, brain parcellation is a crucial prerequisite. Two parcellation branches are anatomical parcellation and functional parcellation. Anatomical parcellation is limited due to incredibly labor and time intensive effort to create one. Functional parcellation is most often custom defined and therefore lacks the ability to generalize to multiple use cases. In addition to that, functional parcellation is limited by the inconsistency and lack of standardized criterion to evaluate it. In our work, we propose a novel functional parcellation that can generalize well across different uses without complicated preprocessing, or mathematical formulations but based on a data driven machine learning method.

Disclosures: J. Park: None. **J. You:** None. **Y. Yoon:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.19/KK54

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

Support: NIH Grant R00EY031333

Title: PHASOR a semi-automated pipeline for stimulus-gated hidden Markov modeling of multielectrode retinal population activity

Authors: *M. SHAIK[1], S. CHEN[3], J. JIN[2], D. BABINO[1];
[2]Neurosci. and Ophthalmology, [1]SUNY Upstate Med. Univ., Syracuse, NY; [3]Upstate Med. Univ., SYRACUSE, NY

Abstract: Latent-state analyses of retinal ganglion cell (RGC) population activity are powerful but labor-intensive, requiring manual stimulus alignment, model-order selection, and cell-type annotation that limit reproducibility and throughput. We present PHASOR (Population HMM Analysis of Stimulus-locked Output in the Retina), a semi-automated pipeline that converts raw multielectrode array (MEA) recordings into validated hidden Markov model (HMM) descriptions of population activity. When data are acquired with a pre-programmed 2 Hz full-field sinusoidal contrast stimulus, the pipeline computes the Fourier transform of the population response and verifies modulation power at the known stimulus frequency, automatically setting the analysis window and phase reference where a stimulus-locked response is expected; recordings lacking this signature are flagged for review. It then fits an HMM with Chow-Liu tree emissions, selects state number by held-out likelihood, and labels each latent mode by its dominant cell type and preferred stimulus phase. Standardized outputs include phase clocks, per-state phase-locking, transition statistics, and cross-condition comparisons. We validated PHASOR in mouse retina across a graded perturbation series spanning loss, blockade, and photoswitch remodeling of structured activity: wild-type retinas yield the expected conserved mode vocabulary; selective ON-bipolar blockade with L-(+)-2-amino-4-phosphonobutyric acid (L-AP4) produces a quantified, reversible collapse of the mode structure (per-state phase-locking R ~0.83 to ~0.34 across four retinas; recovery on washout); untreated rd1 photoreceptor-degenerate retinas show abolished stimulus-locking (R ~0.1); and rd1 retinas treated with the photoswitch DENAQ (diethylamino-azobenzene-quaternary ammonium) enter a distinct regime of increased mode switching and shorter state dwell times, a more dynamically variable landscape rather than a return to wild-type stimulus-locked structure. Across all conditions the pipeline reports the same standardized metrics, distinguishing intact, degraded, and treatment-remodeled population dynamics. By coupling automatic stimulus-frequency gating to standardized HMM fitting and reporting, PHASOR turns an ad hoc analysis into a reproducible, perturbation-ready assay for retinal population coding and a quantitative readout for evaluating vision-restoration therapies.

Disclosures: M. Shaik: None. **S. Chen:** None. **J. Jin:** None. **D. Babino:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.20/KK55

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

Support: Nancy Lurie Marks Family Foundation

Title: Modeling stochastic evolutions of naive exploratory and error-correction learning with inverse-kinematics and dynamics equations of naturalistic arm motions with redundant degrees of freedom

Authors: *J. VEGA LEIVA[1], J. VERO[2], E. B. TORRES[3];
[1]Ctr. for Biomedicine Imaging and Modeling, Piscataway, NJ; [2]Cognitive Sci., Rutgers Univ., Matawan, NJ; [3]Psychology Dept, Rutgers Univ. Dept. of Psychology, Piscataway, NJ

Abstract: Current AI reinforcement learning models rely on error-based optimization whereby the reference to compute the error is given. This form of error-correction learning cannot account for the type of naïve exploratory learning that we perform towards the self-discovery of such reference signals. In this work, we model the process of naïve exploratory learning to identify the reference signal starting from an equiprobable state where all future events are weighted equally, the signal-to-noise ratio is high and no target yet exists (Vaskevich and Torres, 2022). We extend our former deterministic geometric model (Torres and Zipser, 2002) to a stochastic formulation of the inverse kinematics problem addressing Bernstein's degrees of freedom redundancy problem. A locally linear isometric embedding solution is offered via a PDE with orbits that are geodesics in the extrinsic space where the hand rotates and translates and corresponding geodesics in the intrinsic space of joint angles (JA) combined with the Boltzman distribution to map different surprising vs. targeted error-correction states across the peripersonal space and in both the task relevant and the task incidental manifolds of JA. In the context of agentic learning, *i.e.,* motor learning that maximizes surprising events (without instructions) and leads to the self-discovery of the reference target for action (Torres et al. 2013), we show the evolution of the Boltzman process and model the corresponding dynamics. Then we use empirical data from neurotypicals and autistic children to assess the process of reference target self-discovery and compare it to the modelled process. We first report that children on the spectrum of autism (25 non-speakers) can attain the self-discovery of the goal without instructions and follow similar learning kinematics trajectories as neurotypical children (10 matched in age and sex) albeit with different initial stochastic landscape featuring elevated random noise. Through this form of agentic learning, they attain noise cancelation and predictive control improving as well motor coordination. Further we report on their dynamics portrays and evaluate our model's discrepancies with the empirical data. The children's data (autistic and neurotypicals) are compared to those of 20 undergraduates to ascertain signatures and stochastic rules of both motor kinematics and motor dynamics variability across maturation stages of the human nervous systems. We discuss the implications of our work for the development of practical solutions to teach communication methods (mediated by unconstrained pointing) to non-speakers with a diagnosis of ASD.

Disclosures: J. Vega Leiva: None. **J. Vero:** None. **E.B. Torres:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.21/KK56

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

Support: Nancy Lurie Marks Family Foundation

Title: Kinematic Signatures of Self-Discovered Motor Goals in an Active Sensing Task

Authors: *J. VERO[1], E. B. TORRES[2];
[1]Rutgers Univ., Matawan, NJ; [2]Psychology Dept, Rutgers Univ. Dept. of Psychology, Piscataway, NJ

Abstract: Skilled action often emerges without instruction: agents explore, find what works, and consolidate it. Models of naive exploratory learning cast this as a drift from an equiprobable, high-signal state with no reference target toward a predictive, low-randomness one (Torres & Zipser, 2002; Torres et al., 2013; Vaskevich & Torres, 2022). Yet the kinematic signatures of this unknown-to-learning-to-learned transition, the search strategies driving it, and the gap between what learners do and what they can articulate recalling what they did, remain poorly characterized.

Twenty healthy adults (age 18-30 yr) were recorded (Polhemus Liberty, 4 sensors 240Hz) on the dominant arm (middle-finger, forearm, upper-arm, shoulder). Given no hint about the trigger, participants had to self-discover that holding sensor 1 inside an invisible spherical region of peripersonal space (called agentic-learning region, ALR) toggled the playing of a video ON-within the ALR and OFF-outside, pausing it on exit. Each completed three trials with a constant-radius sphere at one of three locations (ipsilateral, midline, contralateral): a 3-min unguided, wondering exploration phase, then a feedback-free verbal explanation and 30-s recall-demonstration of the inferred action. Reward state, region geometry, and entry/exit events were logged with kinematics, screen and arm visible; verbal reports were transcribed. We ask three questions. (1) Exploration: we quantify search strategy with spatial probing metrics and volumetric coverage, distinguishing exploration (mapping the full region) from exploitation (re-triggering reward at one point). (2) State signatures: segmenting by reward history into unknown, learning, and learned epochs, we compare movement smoothness and submovement count, and characterize micromovement parameter trajectories, in both extrinsic end-effector and intrinsic joint-angle coordinates, testing a predicted shift from a high noise-to-signal ratio (NSR), memoryless regime toward a low-NSR, predictive one. (3) Knowledge-action dissociation: we relate the overlap of demonstrated occupancy with the true region to the semantic accuracy of transcripts and to exploration strategy.

We offer a kinematic account of how an unknown motor goal is discovered, refined over time, and verbalized, linking self-guided search to skilled action and exposing dissociations between cognitive knowledge and motor skill. The framework connects motor control to cognition and memory, informing models of agentic learning and its translation to non-instructed skill acquisition, including communication in non-speaking individuals.

Disclosures: J. Vero: None. **E.B. Torres:** None.

Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

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Program #/Poster #: PSTR117.22/KK57

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

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BrainsCAN Postdoctoral Fellowship (CFREF)

Title: Inferring distributed computational mechanisms from multi-area neural recordings

Authors: *C. VERSTEEG[1], M. KASHEFI[3], J. A. MICHAELS[3,4,7], A. PRUSZYNSKI[5,4,6], C. PANDARINATH[8,2,9];
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Abstract: Understanding how computation is distributed across interacting brain areas requires separating the dynamics intrinsic to each area from the signals communicated between them. Existing methods have limitations that make them difficult to interpret: single-area dynamics models often suffer from hallucinations and/or leave external inputs underdetermined, while communication-only models lack an explicit notion of dynamics. We introduce DynISys (Dynamically-Interacting-Systems), a multi-area latent dynamics model that infers per-area dynamics, structured inter-area communication, and external inputs directly from simultaneously recorded spiking activity. DynISys combines neural-ODE dynamics, injective normalizing-flow readouts, and low-dimensional inter-area communication channels, resulting in expressive, trustworthy, and interpretable models.We applied DynISys to simultaneous PMd and M1 Neuropixels recordings from a monkey performing a sequential reaching task. In this task, the upcoming target is visible during the current reach, which helps disambiguate neural activity patterns associated with planning from those involved with execution. DynISys reconstructed single-neuron responses and single-trial state-space trajectories with high fidelity. We found that DynISys was resistant to feature hallucination: unlike a comparable RNN-based multi-area model, the timing of task information appearing in DynISys latent dynamics models paralleled when that information appeared in the neural data itself. DynISys also captured the flow of information between areas, inferring a unidirectional transfer of the motor plan from PMd to M1 that recapitulated the order in which target information emerged across areas. Finally, DynISys

also allowed us to interrogate the inferred dynamics for computational mechanisms. First, we found that during the preparatory phase of individual trials, the inferred M1 dynamics contained a single fixed point whose location encoded the upcoming reach for that trial. The location of this fixed point was determined largely by the inferred inputs to M1 from PMd. We found that in-silico perturbations of these inputs led to predictable effects on the location of M1's fixed points, putting forward an experimentally testable hypothesis of the mechanism of PMd/M1 interactions during motor planning. By separating each area's intrinsic dynamics from the signals exchanged between them, DynISys allows researchers to distill multi-area recordings into interpretable accounts of distributed computation.

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Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.23/KK58

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

Support: NIH 1R01AG079345

Title: Single-subject P300 detection via joint state-space estimation of oscillatory background and evoked response

Authors: *S. TOU[1], P. DAS[3], M. HE[2], P. L. PURDON[4];
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Abstract: Event-related potentials (ERPs) are well-established neural indices of attention and stimulus categorization(1), but reliable estimation within a single recording remains an unsolved problem. Conventional trial averaging requires hundreds of trials to overcome background EEG activities at the group level. The absence of methods that estimate individual ERPs reliably from short recordings makes bedside ERP assessment infeasible.We developed a state-space ERP (SS-ERP) framework that jointly estimates the oscillatory EEG background (a sum of stochastic oscillators) and the evoked waveform (an AR(1) random-walk process) under a single variational-Bayes EM algorithm. By separating background and evoked components at convergence, SS-ERP returns a posterior distribution over the ERP waveform at every time point.To test individual-level detectability at scale, we applied SS-ERP to all 55 subjects of the Won et al. (2022) visual P300 dataset(2) (~1500 standard and ~300 target trials per subject) and computed per-subject Cohen's d for the target-minus-standard difference in the 250-500 ms window. SS-ERP yielded per-subject d of 1.37 (Cz), 1.25 (Pz), 1.31 (PO3), 1.32 (PO4) — all in the large-effect range — versus 0.17, 0.10, 0.16, 0.18 for conventional averaging. We further re-

fit each subject on non-overlapping subsets of ~30 target and ~150 standard trials; SS-ERP per-subject d remained in the large-effect range — 1.50 (Cz), 0.98 (Pz), 0.92 (PO3), 0.86 (PO4) — while conventional averaging stayed at 0.21, 0.11, 0.14, 0.14. Joint state-space modeling of oscillatory background and evoked response shifts the P300 from a cohort-level statistic to a within-subject readout with quantified posterior uncertainty, removing a primary barrier to single-recording ERP assessment.1.Polich J. Updating P300: An integrative theory of P3a and P3b. Clinical Neurophysiology. 2007 Oct;118(10):2128-48. doi:10.1016/j.clinph.2007.04.019 PubMed PMID: 17573239; PubMed Central PMCID: PMC2715154.
2.Won K, Kwon M, Ahn M, Jun SC. EEG Dataset for RSVP and P300 Speller Brain-Computer Interfaces. Sci Data. 2022 Jul 8;9(1):388. doi:10.1038/s41597-022-01509-w PubMed PMID: 35803976; PubMed Central PMCID: PMC9270361.

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Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.24/KK59

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

Title: Interpretable, Data-Driven MRI Quality Control Using Deep Learning

Authors: *K. SARULLO[1], M. HELMER[2], F. FARAHANI[3], J. BURT[1], J. JI[1], R. ABDOLLAHI[4], J. PATEL[1], R. DATTA[5], Z. S. SAAD[5], G. M. WITTENBERG[6], A. ANTICEVIC[1];
[1]Johnson & Johnson, Cambridge, MA; [2]Johnson & Johnson, Denver, CO; [3]Johnson & Johnson, Spring House, PA; [4]Johnson & Johnson, Leiden, Netherlands; [5]Johnson & Johnson, San Diego, CA; [6]Johnson & Johnson, Titusville, NJ

Abstract: Non-invasive magnetic resonance imaging (MRI) of human brain structure and function plays a central role in neuroscience research and drug development, quantifying target engagement and enabling patient stratification and biomarker development in neurodegenerative and neuropsychiatric disorders. Though modern neuroimaging processing pipelines are largely automated, post-processing dataset curation—a critical step conventionally referred to as quality control (QC)—remains a major bottleneck in large-scale studies and clinical trials with neuroimaging endpoints. QC is typically a laborious and subjective process, during which neuroimaging experts inspect visual representations (images) of pipeline outputs for each study participant, often at multiple intermediate processing stages, for evidence of registration errors, segmentation errors, or uncorrected image-acquisition artifacts. To address the critical unmet need for automated, accurate, and transparent QC, we developed a convolutional neural network that provides interpretable, data-driven outputs within our MRI-processing workflows. We aggregated T1weighted MRI scans from multiple studies and sites into a dataset of 2,481 images,

manually annotated by experts following standardized QC criteria and split into training and testing sets (80/20). During training, the model learns features within localized image patches that inform binary pass/fail predictions; at inference time, learned features are compared against patches in unseen in-sample test images. The model achieved 97% accuracy on heldout test images—91% accuracy on a balanced dataset—while providing human-interpretable explanations for each prediction, substantially reducing manual QC burden and allowing experts to focus on a fraction of cases where the model's confidence in its predictions was below an acceptable threshold. Critically, scalable QC systems enable curation of massive neuroimaging datasets where manual QC is infeasible, as well as eliminate a major source of variance—variability between experts—that is difficult to quantify and flows into all downstream statistics. Given sufficient data, our framework is readily extensible to modalities beyond T1weighted imaging. Our findings demonstrate that deep learning can largely automate neuroimaging QC without sacrificing performance for interpretability, important for auditable endpoints in regulatory contexts. Through scalable neuroimaging workflows, automated QC systems can accelerate scientific and clinical neuroscience research and shorten development timelines for novel therapeutics.

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Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.25/KK60

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

Support: NIDCD R21 DC021013

Title: Self-Supervised Pretraining on Intracranial EEG Improves Downstream Semantic Decoding

Authors: *A. J. SKITOWSKI[1], M. SABER[2], S. MATHEW[2], D. AHMED[3], W. L. GROSS[4]; [1]Biophysics, [3]Biomed. Engin., [4]Anesthesiol., [2]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Intracranial electroencephalography (iEEG) provides a unique opportunity to record brain activity with a high degree of spatial and temporal resolution. However, recordings are usually collected from patients with specific clinical needs, resulting in heterogeneous coverage of the brain and limited labeled data. This limits the development of large decoding models that typically require a substantial amount of labeled data to achieve optimal performance. To address these issues, we propose a Large EEG Model (LEM) pretrained on a large set of unlabeled iEEG recordings, enabling the model to learn transferable representations of neural activity. We constructed a 49M-parameter masked autoencoder model trained using self-supervised learning to reconstruct masked input data. Training data consisted of over 600 hours of normalized iEEG recordings collected from 96 patients, downsampled to 500 Hz. Random time windows of 4 s using subsets of 32 random electrodes were tokenized into 40-ms windows using a shallow convolutional neural network. These tokens were then fed into a 4-layer axial transformer network with multiple global readout tokens concatenated to the end of the sequence. Encoded representations were reconstructed with a shallow MLP decoder. To encourage transfer learning, masking was applied to 30% of the data, and whole electrodes were masked 10% of the time. The model was trained using a Smooth L1 reconstruction loss applied to the masked portions of the input. After pretraining, the frozen model was applied to unseen task-based iEEG data collected from 5 subjects who performed a semantic categorization task. Subject specific linear decoders were trained for each subject, and performance using raw iEEG signal features was compared with performance using the pretrained LEM representations. The pretrained LEM improved semantic decoding performance from 0.503 to 0.607 (mean percentile rank; $p = 0.0407$). These results demonstrate that self-supervised pretraining on large unlabeled iEEG datasets can produce representations that improve downstream cognitive decoding.

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Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.26/KK61

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

Support: Wellcome Trust Grant 226486/Z/22/Z
Center for Mesoscale Connectomics Grant NINDS UM1NS132207
Data Coordination Center Grant NINDS U24NS140384
Amazon Web Services Open Data Sponsorship Program

Title: large language models for extracting white matter findings from the diffusion MRI literature

Authors: *S. KIILU[1], K. L. RAY[1], F. PESTILLI[2];
[2]Psychology, [1]The Univ. of Texas at Austin, Austin, TX

Abstract: The diffusion MRI (dMRI) literature is growing fast, outpacing the human capacity to synthesize it. Findings on human white matter tracts are scattered across thousands of dense, technical articles, and the white matter community lacks consensus on how to name and delineate them. These two bottlenecks have long slowed the translation of a vast dMRI literature into actionable, quantitative data. Large language models (LLMs) can now read this kind of specialized biomedical text, and large-scale automated extraction looks feasible. Here, we focus on dMRI studies of dementia and related disorders. We chose this domain because the relevant white matter microstructural changes have been studied extensively, giving us a rich literature against which to test our extraction pipeline. To address the lack of standardization in tract naming, we built a white matter look-up table (LUT) of canonical tracts grounded in the Uberon and SNOMED CT biomedical ontologies, and a manually annotated benchmark of 622 articles covering 14 variables across bibliographic, technical, and anatomical categories. Our extraction pipeline reaches F1 > 0.84 on clinical metadata such as subject demographics and neurodegenerative disease type. White matter tracts are the hardest variable, and incorporating the LUT raises GPT-5-mini's F1 by 21 points (from 0.47 to 0.68). These results lay a foundation for automated meta-analysis of the dMRI literature, and more broadly for any biomedical domain where reasoning-capable LLMs can be combined with curated vocabularies to scale literature synthesis.

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Poster

PSTR117: Decoding Large-Scale Neural Dynamics: Models, States, and Whole-Brain Population Computation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR117.27/KK62

Topic: G.02. Neuroendrocrine Processes and Behavior

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NSF/CAREER Grant 2235858

Title: Designing a high-throughput, customizable, and extensible neuroeconomic framework for the study of context-driven decision-making

Authors: *R. IBÁÑEZ ALCALÁ[1], L. RAKOCEVIC[2], C. HEATON[1], K. GOOSENS[3], A. FRIEDMAN[4];
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Abstract: Variability caused by personalized aspects of choice like subjective valuation of decision-making (DM) variables, past experiences, and motivations, is an obstacle often faced in DM studies. One must account for this, enable direct comparisons of choice patterns, and identify interactions between choice selection and internal states (hunger, pain, etc.), in various contexts. Currently, paradigms such as the Iowa Gambling Task or the Balloon Analogue Risk Task can offer granular insights into components of risk, but often rely on rigid environments with limited ability to account for individual variability in response to task stimuli in different contexts. To address these needs in one framework, we developed the Human Model for Analyzing Neuroeconomic Situations (HUMANS), a suite of customizable software designed around principles of neuroeconomics to quantify DM patterns. In our approach, positive and negative motivators are user-specific and paired in tradeoffs that may be approached or avoided. Users rank motivators by pleasant or unpleasantness, allowing us to abstract specific items into subjective value levels, enabling comparisons based on stimulus valuation. Our custom web application serves as a cross-platform frontend for our framework that can be deployed online. In it, our tasks guide users through written stories across morally ambiguous, social, probabilistic, and cost/benefit contexts, creating rich, individually variable datasets. Our story-based task structure provides an inexpensive avenue to track DM patterns, and is extensible to new contexts. New stories can be reviewed using our story verifier app for quality control. We support external eye tracking and heart rate monitoring hardware to track physiological changes during tasks. All data are anonymized, synchronized with a custom script, and stored in a PostgreSQL database during task performance. User-specific data is tracked server-side and identified via an encrypted cookie and a randomized ID number to protect privacy. As validation, we tested whether we would detect variations in user choice across task contexts. The data from 250 participants were distilled into psychometric functions and heat maps to observe DM patterns, and average approach rates over several trials for each user were compared with a 1-way ANOVA test across task, reward, and cost levels. We found that the approach rates were significantly different across reward levels (df=3, p=6.18e-44), cost levels (df=3, p=3.9e-41), and tasks (df=5, p-val=2.71e-28), suggesting that context created choice pattern variations. Generally, approach rate increased with increasing reward and decreasing cost.

Disclosures: R. Ibáñez Alcalá: None. **L. Rakocevic:** None. **C. Heaton:** None. **K. Goosens:** None. **A. Friedman:** None.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.01/KK63

Topic: J.08. Methods to Modulate Neural Activity

Support: Abbott Funding

Title: A Hierarchical Control Model for Closed-Loop DBS in Parkinson's Disease:Scoping the Scientific and Computational Requirements

Authors: *J. T. DUBUCLET[1], Y. T. PATHAK[2];
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Abstract: To establish a theoretical framework for biology-informed closed-loop deep brain stimulation (DBS) in Parkinson's disease (PD), we rigorously surveyed the literature to define the scientific and computational requirements for a hierarchical model. In this paradigm, slow-moving systemic biological states (e.g., metabolic factors, inflammatory tone) parametrically modulate a real-time, fast-acting neurophysiologically-driven controller.
Current adaptive DBS systems primarily utilize single biomarker controllers (e.g., STN beta-band power). While effective, this unimodal approach fails to fully capture biological heterogeneity driving symptom variability and correlates poorly with tremor and gait dysfunction. We propose a hierarchical model to address these gaps, validating its core assumptions through this synthesis.
We conducted a cross-disciplinary synthesis of PubMed, Scopus, and Web of Science (2014-2024). Screening over 300 records, 42 studies underwent qualitative evaluation for three architectural components: (1) quantifiable "slow" systemic state variables; (2) robust "fast" neurophysiological control signals; and (3) mathematical frameworks integrating multi-scale biosignals.
Our synthesis confirms technical precedents for each component exist in isolation. Literature provides strong quantitative evidence for systemic state markers (e.g., glycemic variability) and validated neurophysiological signals (e.g., LFP beta, cortico-subthalamic coherence). Critically, data-driven state-space models offer a computationally tractable framework for fusing these disparate time-series. The principal barrier is practical: the lack of concurrent, multi-scale datasets from a single cohort to parameterize an integrated model.
A hierarchical control architecture for Biology-Informed Closed-Loop DBS is conceptually validated by existing, disconnected streams of literature. By systematically scoping requirements and identifying a viable computational approach, this synthesis provides foundational evidence for a dedicated discovery study. The immediate opportunity lies in designing an experiment to capture concurrent data, bridging the gap from a theoretical framework to an empirically-grounded, testable model.

Disclosures: J.T. Dubuclet: A. Employment/Salary (full or part-time):; Abbott. **Y.T. Pathak:** A. Employment/Salary (full or part-time):; Abbott.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.02/KK64

Topic: J.08. Methods to Modulate Neural Activity

Support: National Science Foundation (NSF) GCR Program under Award No. GR1057743
National Eye Institute of the National Institutes of Health under Award No. EY035375, an unrestricted grant to the Department of Ophthalmology from

Research to Prevent Blindness
Walt and Lily Disney RPB Amblyopia award

Title: Computationally Guided Extra-Ocular Electrical Stimulation Enables Activation and Reversible Suppression of Retinal Output In Vivo

Authors: *O. SHARAFI[1], A. SIMONYAN[2], J. YANG[2], H. MOKHTARI DOWLATABAD[1], P. PAHLAVAN[1], B. LIN[2], W. LUK[1], J.-M. C. BOUTEILLER[3], K. K. GOKOFFSKI[2], G. LAZZI[1]; [1]USC, Los Angeles, CA; [2]Univ. of California, Irvine, Irvine, CA; [3]Biomed. Engin., USC / INDRC, Los Angeles, CA

Abstract: Electrical stimulation of the visual system offers a potential strategy for modulating retinal output, but selective retinal targeting remains challenging due to off-target stimulation of surrounding neural structures. We combined computational modeling, behavioral testing, and in vivo electrophysiology to develop and validate an extra-ocular stimulation strategy that enables bidirectional modulation of retinal output while minimizing stimulation of central visual structures.

Using an anatomically informed Admittance Method model, we screened multiple electrode configurations and identified that a perineural optic nerve (ON) electrode paired with a circumferential scleral (SCL) electrode generated strong retinal electric fields (~10^3 V/m) while minimizing field spread to the brain (~10^{-4}-10^{-3} V/m). Behavioral testing in awake rats revealed a broad safety margin, with tolerated stimulation amplitudes reaching up to 1600 µA-more than an order of magnitude above thresholds required for retinal modulation.

The optimized ON-SCL configuration was validated in vivo (n=10 rats) using visual cortical local field potential recordings. Low-frequency asymmetric charge-balanced stimulation reliably activated the visual pathway, producing visual cortical responses approaching the magnitude of natural light-evoked activity at stimulation amplitudes of ~100 µA. We then tested whether high-frequency stimulation paradigms previously shown to suppress retinal ganglion cell activity ex vivo could produce functional suppression of retinal output. Continuous 5 kHz and 10 kHz sinusoidal stimulation significantly attenuated light-evoked cortical responses, with suppression emerging between 75-100 µA and increasing in a dose-dependent manner stimulation amplitude. At higher amplitudes, cortical responses were reduced to approximately 60-70% of baseline at 5 kHz and 20-30% of baseline at 10 kHz. Importantly, responses returned to baseline after stimulation ceased, indicating reversible modulation without persistent suppression.

These findings demonstrate that computationally optimized extra-ocular stimulation can both activate and reversibly suppress retinal output in vivo. This approach establishes a practical framework for bidirectional retinal circuit modulation and constitutes a viable foundation for future visual prosthetic and vision-restoration strategies.

Disclosures: O. Sharafi: None. **A. simonyan:** None. **J. Yang:** None. **H. Mokhtari Dowlatabad:** None. **P. Pahlavan:** None. **B. Lin:** None. **W. Luk:** None. **J.C. Bouteiller:** None. **K.K. Gokoffski:** None. **G. Lazzi:** None.

Poster

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Program #/Poster #: PSTR118.03/KK65

Topic: J.08. Methods to Modulate Neural Activity

Support: Xecs research and innovation program (XECS241001)

Title: A Spatiotemporal Stimulation and Blocking Strategy for Selective Peripheral Neuromodulation

Authors: *P. SCHNEPEL[1], A. CRESPO[1], G. YORDANOVA[1], Y. BEZWORK[1], N. ROSSETTI[1], N. JAYAPRAKASH[2], J. WONG[2], T. DATTA[2], S. ZANOS[2], V. MIHAJLOVIC[1]; [1]imec, Eindhoven, Netherlands; [2]Feinstein Inst. For Med. Res., Roslyn Heights, NY

Abstract: Peripheral nerve stimulation (PNS) approaches are frequently hindered by the structural and physiological complexity of nerve bundles, which can limit therapeutic outcomes and induce undesirable side effects. Enhancing both the spatial precision of stimulation - targeting specific regions within a nerve - and functional selectivity - addressing distinct organ-specific fiber populations - has the potential to substantially improve PNS efficacy.In this study, we present an approach that enables fine control over nerve activation and blocking by integrating high-frequency stimulation waveforms with independently applied anodal blocking. This configuration allows modulation of spatio-temporal activation patterns through coordinated cathodal stimulation and anodal inhibition. Using a simplified earthworm nerve model, we demonstrate that compound action potentials (CAPs) can be directionally suppressed by carefully adjusting the timing and amplitude of blocking pulses delivered via a separate anodal electrode. Our results further show that the interplay between stimulation waveform characteristics and the temporal alignment of stimulation and blocking signals provides precise control over CAP propagation. By jointly optimizing these parameters, selective modulation of different fiber populations is achievable, such as activation of either slow- or fast conducting fibers. Finally, we extended the concept to a more complex mammalian model, where we used multi-contact cuff electrodes to deliver timed stimulation and anodal blocking to the sciatic nerve of a rat. We observed a marked reduction in EMG (electromyography) activity in several muscles for specific combinations of anodal blocking amplitude, timing and stimulation waveform.Overall, the findings highlight that combining tailored stimulation waveforms with temporally coordinated anodal blocking offers a powerful framework for achieving both spatial and functional selectivity in PNS. We show that this strategy can be extended to more complex mammalian nerve systems, where precise spatio-temporal control becomes crucial. The proposed methodology thus represents a promising pathway toward more selective and effective neuromodulation therapies.

Disclosures: P. Schnepel: None. **A. Crespo:** None. **G. Yordanova:** None. **Y. Bezwork:** None. **N. Rossetti:** None. **N. Jayaprakash:** None. **J. Wong:** None. **T. Datta:** None. **S. Zanos:** None. **V. Mihajlovic:** None.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.04/LL1

Topic: J.08. Methods to Modulate Neural Activity

Title: Process for creating porous structure for arbitrary shape bone surrogates

Authors: L. DANKOVICH IV[1], C. SINKS[2], E. WILLETTS[3], W. GREEN[1], ***W. HAIRSTON**[4]; [1]DEVCOM Army Res. Lab., Aberdeen Proving Ground, MD; [2]DEVCOM Army Reserach Lab., Aberdeen Proving Ground, MD; [3]Energetics Technol. Ctr., Aberdeen, MD; [4]US Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: While surrogate materials have been used to mimic the mechanical properties of bone, little focus has been given to recreating the electrical / conductive properties of live material. This is necessary for phantoms (e.g. skull) used in verifying electrical or magnetic conduction (e.g. tACS, TMS) where both the micro- and bulk properties are relevant. Given that most bone-mimicking materials are solid while bone is a porous conductor by nature, here we explore the feasibility of creating a printable porous internal structure that can be infused with higher-conducting gels and describe a process of creating and validating a porous, heterogeneous matrix within an arbitrary shaped object.

A Blender plugin was developed to create user-definable porosity via a Voronoi matrix - tessellated fields where 'seeds' are placed over a given space divided into cells where all points within the space are closer to a given seed than any other. Each cell defines a pore network's geometry by assignment as void space or solid, with two variables assigned per network. "Scale" indicates how many seeds should be placed in a given space, affecting the typical size of cells (Fig A) while "Density" defines the percentage of cells at a given distance from the surface. This allowed for either making uniformly porous structures or those in which porosity more closely emulated the gradients found in bone (see B & C for a sample).

This routine was applied to cubic (1cm) and spherical (5 cm) hollow models and SLA-printed in Formlabs Rigid10k (60% density depicted in Fig D). MicroCTs of samples were used to initially confirm effective removal of uncured resin, then validating model printing accuracy based on voxel-wise comparison to define a functional size minima. Results to date suggest reasonable recreation accuracy for simple structures with ongoing work addressing application to more complex arbitrary shapes (skull, multi-layered trabecular bone). This success, in combination with addition of ionically-tuned gelatins to create a bulk conductivity holds a promise for useful surrogates for a variety of applications.

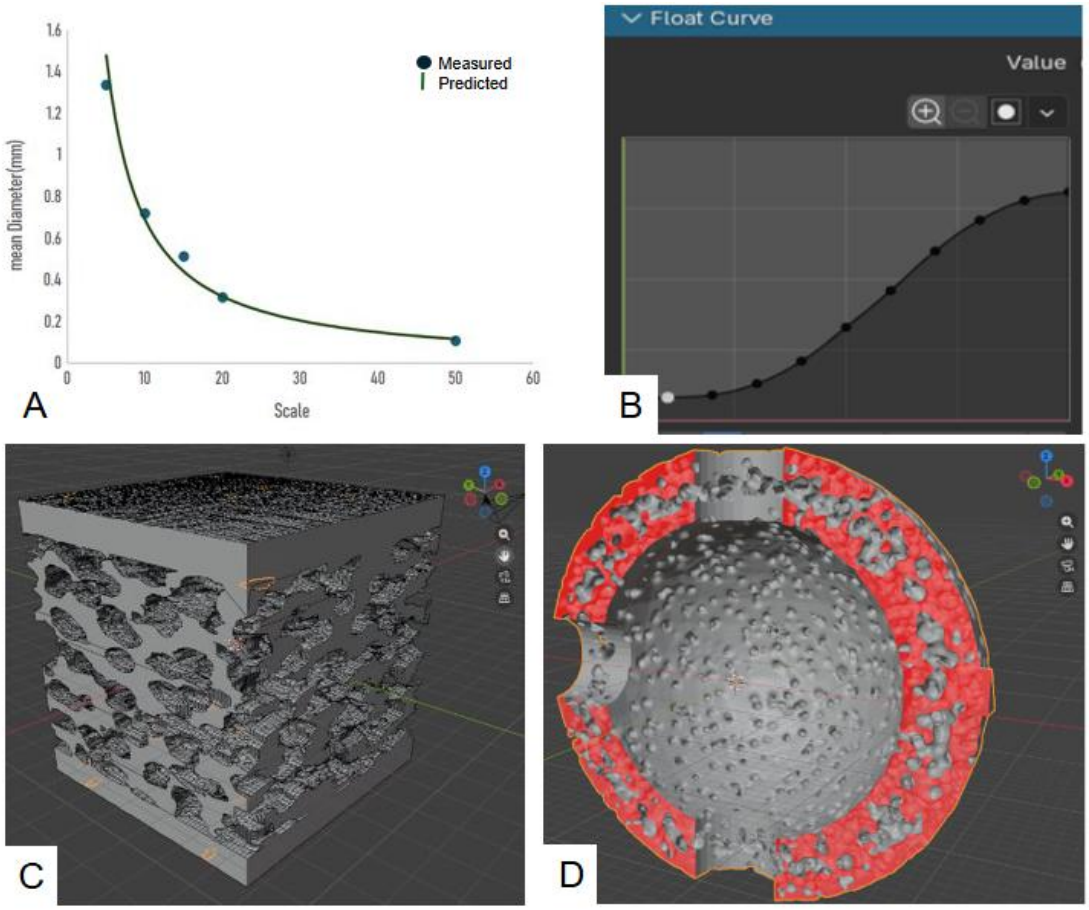


Figure 1: A) By setting scale as an input, pore size can be controlled. Given expected pore sizes in bone and limitations of printer 0.15 is a resonable value, B) by setting discrete points on the porosity plot a curve can be generated representing the porosity anticipated in human bone C) the box represents a cubic cross section emulating bone D) the sphere represents a proof of concept for generating arbitrary shapes such as skulls

Disclosures: L. Dankovich IV: None. **C. Sinks:** None. **E. Willetts:** None. **W. Green:** None. **W. Hairston:** None.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.05/LL2

Topic: J.08. Methods to Modulate Neural Activity

Support: KIST Grant 26Z9002
NRF Korea Grant RS-2024-00337573

Title: Non-Invasive High-Frequency Patterned Electrical Stimulation Restores Cognitive Function in Alzheimer's Disease Model

Authors: *S.-H. PARK, S. LEE;
Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract: Non-invasive electrical stimulation has emerged as a promising approach for modulating neural activity and alleviating pathological processes associated with neurodegenerative disorders. In Alzheimer's disease (AD), stimulation modalities such as transcranial direct current and alternating current stimulation (tDCS/tACS) have demonstrated beneficial effects on cognitive function and disease-related pathology. However, conventional stimulation approaches primarily target superficial cortical regions and often require continuous stimulation to achieve therapeutic effects. These characteristics may limit effective engagement of deeper neural circuits while increasing overall energy exposure and stimulation-related side effects. To address these challenges, we developed a novel high-frequency patterned electrical stimulation strategy employing structured burst delivery within a low-duty-cycle architecture. This approach was designed to reduce average energy exposure while maintaining neuromodulatory efficacy and potentially facilitating engagement of broader neural networks. The therapeutic potential of this stimulation paradigm was evaluated in a transgenic AD mouse model. Male 5XFAD mice and age-matched wild-type littermates were assigned to sham, tACS, or novel stimulation groups and received repeated non-invasive stimulation over an extended treatment period. Behavioral performance was assessed using tests of anxiety, recognition memory, and spatial learning. Following behavioral assessments, brain tissues were collected for histological evaluation of AD-related pathology. Stimulated AD mice exhibited improved cognitive performance compared with sham-treated controls, including enhanced recognition and spatial memory. Animals receiving the novel stimulation also displayed reduced anxiety-like behavior without evidence of adverse behavioral effects. Histological analyses revealed attenuation of AD-associated neuropathological burden such as amyloid-beta and p-Tau in brain regions involved in learning and memory. Collectively, these findings demonstrate that a high-frequency patterned electrical stimulation strategy can improve cognitive function and mitigate AD-related pathology in 5xFAD mice. By combining structured high-frequency stimulation with reduced energy exposure, this approach may provide an efficient and well-tolerated alternative to conventional stimulation paradigms while potentially enabling engagement of deeper and more distributed neural circuits.

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

Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.06/LL3

Topic: J.08. Methods to Modulate Neural Activity

Title: Picosecond pulsed electric fields modulate metabolic response in Huntington’s Diseased Cells

Authors: *A. U. ANTHONY, M. A. TARDIF-KUNK, A. WOLTER, P. A. MOLLICA;
Sch. of Med. Diagnos. & Translational Sci., Old Dominion Univ., Norfolk, VA

Abstract: Huntington Disease (HD) is a devastating and progressive autosomal dominant neurodegenerative disorder characterized by polyglutamine (PolyQ) aggregation and mitochondrial dysfunction. Current therapies slow clinical progression but do not restore function, and no non-invasive strategies exist to directly modulate polyQ aggregation. Picosecond pulsed electric fields (psPEF) are ultra-short bursts of high-intensity electric fields capable of modulating intracellular structures and inducing distinct cell death pathways without overt membrane poration. However, whether psPEF produces differential functional responses in mHTT-expressing neural cells versus isogenic wild-type controls remains incompletely defined. In this study, we aimed to determine whether psPEF-induced disaggregation could rescue metabolic activity without compromising cell viability in isogenic wild-type (wtHTT) CH00066 and mutant (mHTT) CH00076 rat-derived striatal progenitor cell lines. We seeded cells at matched densities and maintained them in DMEM supplemented with 10% FBS and 1% ABAM at 33 °C with 5% CO_2. Using a custom 3D bioprinter-based stimulation platform, we exposed the cells to psPEF at 0 (sham), 20, and 40 kV/cm (pulse width = 660 PS) in a non-contact configuration. We quantified cellular metabolic activity over time using an Alamar Blue fluorescence assay. Time-course measures demonstrated a genotype-dependent response to psPEF exposure. We observed that psPEF elicited increased Alamar Blue fluorescence in mHTT cells, at 6 and 24 hours post-exposure relative to sham, whereas wtHTT cells showed minimal change across the same time points and exposure conditions. These preliminary results, like those reported in neural stem cells (Petrella et al., 2018), indicate an early, selective shift in metabolic activity capacity in mHTT-expressing cells under the tested psPEF parameters, suggesting that psPEF can modulate cellular metabolic state in a disease-relevant and time-dependent manner. Together, these findings show that psPEF may serve as a therapeutic strategy for the management of PolyQ diseases, offering a new direction for therapeutic development in protopathic-driven conditions.

Disclosures: A.U. Anthony: None. **M.A. Tardif-Kunk:** None. **A. Wolter:** None. **P.A. Mollica:** A. Employment/Salary (full or part-time):; Old Dominion University.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.07/LL4

Topic: J.08. Methods to Modulate Neural Activity

Title: The freely-moving electrophysiological and behavioral evidence of the antinociceptive and analgesic effect of electroconvulsive stimulation

Authors: *J. TREJO, D. IBARRA, Y. B. PENG;
Univ. of Texas at Arlington, Arlington, TX

Abstract: The implementation of electroconvulsive therapy (ECT) has been utilized for many decades since Cerletti and Bini's 1938 development and has since been used to treat major depressive patients who have revealed resistance to other modes of treatment. A few other disorders include schizophrenia and bipolar disorder, and it has even been utilized in patients with chronic pain. Similarly, ECT in humans is known as electroconvulsive shock/stimulation (ECS) in animal models. A powerful electrophysiological tool is known as the local field potential (LFP), and it records the summation of electrical activity of the brain around the tip of an electrode. The LFP can be subdivided into five frequency bands: delta (0.1 - 3 Hz), theta (3 - 7 Hz), alpha (7 - 12 Hz), beta (12 - 30 Hz), and gamma (30 - 100 Hz), and their power is used to reflect the change of specific brain activities. To determine if ECS is effective in alleviating formalin-induced nociception, we recorded continuous LFP in four distinct regions of the male adult Sprague-Dawley rat brain in a freely-moving state: anterior cingulate cortex (ACC), bilateral central amygdala (R-CeA, L-CeA), and the ventral tegmental area (VTA). The hypothesis is that ECS will demonstrate antinociceptive and analgesic properties by suppressing the LFP power and by reducing the formalin-pain behavioral response. In the present study, the LFP was recorded simultaneously with the formalin-pain behavioral test in two conditions: formalin-only (control) and formalin-ECS (experimental). In the formalin-only group after a 10 min baseline recording, under brief isoflurane anesthesia, 3% 50µl formalin was injected into the left hind paw. In the formalin-ECS group, similarly, the rodent was administered a formalin injection followed by 3 ECS stimulations at 50 pulses/s, 0.7 ms, 50 mA for 2 s, with an interstimulus interval of 10 s. In both conditions, the LFP and behavioral activity was then recorded and scored for a full 60 min. The 5 min power spectrum analysis revealed an inhibitory LFP effect post-ECS. Significant differences were found between groups in the ACC, R-CeA, and VTA regions, at most frequency bands, but no significant differences were found in the L-CeA region. In the behavioral testing, results demonstrated significance at the 5-, 10-, and 20-min time-point, with the formalin-ECS group showing a significantly lower behavioral formalin-pain score. The hypothesis is currently supported by both the LFP data and the behavioral data. The findings of this study provide a foundation for potentially exploring the use of this technique in patients who experience pain.

Disclosures: J. Trejo: None. **D. Ibarra:** None. **Y.B. Peng:** None.

Poster

PSTR118: Electrical

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Program #/Poster #: PSTR118.08/LL5

Topic: J.08. Methods to Modulate Neural Activity

Support: National Eye Institute Grant R01EY035008

Title: Closed-loop electrochemical etching of carbon fiber electrodes for intraretinal stimulation

Authors: *J. POSSO, J. G. LETNER, C. A. CHESTEK, J. WEILAND;
Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Intraretinal stimulation has the potential for focal retinal activation due to its placement within the retina. This approach requires electrode contacts that are sharpened for insertion, while maintaining a consistent surface area to allow safe and focal stimulation. Electrochemical etching can produce small, sharp, carbon fiber (CF) microelectrodes, but has shown high variation in electrochemical characterization (Riche et al, 2024). We explore a closed-loop approach using current monitoring of individual CF microelectrodes during electrochemical etching to terminate the applied potential. 8-channel CF microelectrodes, shown in (Riche et al, 2021), were assembled and insulated with Parylene C. CFs were cut to length with a 455 nm laser and then cleaned with O2 plasma, resulting in an uninsulated 160 μm tip. Electrochemical etching used a 3-electrode setup and an electrolytic medium of equilibrated and diluted chromic acid, composed of 0.5 mM K2Cr2O7 | 5 M H_2SO_4 (Riche et al, 2024). Etching was performed on CFs (n = 8) using a 5V potential. The CF's current was monitored, enabling closed-loop feedback to terminate the applied potential when an empirical threshold of 5 μA was reached. Electrochemical impedance spectroscopy measurements and optical images were obtained to determine 1 kHz impedances and tip lengths. The measured 1 kHz impedances and tip lengths for the etched CFs were 805.69 ± 52.00 kΩ and 25.30 ± 9.94 μm, respectively. The etching time was 6.43 ± 1.66 s. Closed-loop electrochemical etching resulted in promising tip lengths for intraretinal stimulation. Etching time variation demonstrated the benefit of the individualized etching approach.

Disclosures: J. Posso: None. **J.G. Letner:** None. **C.A. Chestek:** None. **J. Weiland:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Epic Medical Inc.

Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR118.10/LL7

Topic: J.08. Methods to Modulate Neural Activity

Support: Japan Student Services Organization fellowship
NIH CRCNS R01 MH118929
NSF NCS DRL 2124066
Simons Foundation NC-GB-CULM-00003241-05
Raynor Cerebellum Project

Title: Impact of microstimulation on nearby spiking and gamma-band power in the local field potential

Authors: *D. KANUNGO[1], J. SOLDADO-MAGRANER[2], Y. MINAI[3], B. M. YU[2], M. A. SMITH[4];
[1]Biomed. Engin., [2]Electrical and Computer Engin., [3]Neurosci. Inst., [4]Biomed. Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Neuromodulation therapies such as deep-brain stimulation (DBS) use electrical microstimulation to modulate neural activity, with stimulation parameters largely adjusted by clinicians through trial-and-error to manage symptoms. In chronically implanted clinical devices, intracranially recorded neural activity can inform parameter selection by assessing how stimulation affects neural activity, but typically only includes local field potentials (LFPs). However, our most detailed knowledge of the impact of microstimulation comes from spiking activity, which provides high spatial and temporal resolution, whereas LFPs reflect aggregate activity across larger neural volumes. In the context of causal manipulations, these two signals have largely been studied in isolation. Simultaneously measuring spiking activity and LFP responses to the same stimulation parameters can inform neuromodulation by providing insight into how cortical circuits interact with electrical input. Gamma-band LFP signals are known to relate to local spiking activity, but whether electrical stimulation drives both signals similarly across clinically relevant parameters is unknown. To investigate this, we analyzed recordings from a 96-channel Utah array in the left dorsolateral prefrontal cortex (dlPFC) of an adult male rhesus macaque, with microstimulation delivered across multiple electrode sites at a range of amplitudes (5-25 μA) and frequencies (50-350 Hz). At lower frequencies and amplitudes, stimulation weakly modulated gamma-band LFP and spiking activity, producing spatially heterogeneous patterns of excitation and suppression across the array that were inconsistent across both signals. At higher stimulation frequencies and amplitudes, both signals were positively correlated and showed similar spatial response patterns. In this regime, most stimulation sites produced broad suppression that decreased in strength with distance from the stimulation site. These results suggest that under certain stimulation regimes, gamma-band LFP can inform how neuromodulation impacts local spiking activity, with potential relevance for clinical neuromodulation.

Disclosures: D. Kanungo: None. **J. Soldado-Magraner:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Patent Application No. PCT/US25/47445. **Y. Minai:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Patent Application No. PCT/US25/47445. **B.M. Yu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Patent Application No. PCT/US25/47445. **M.A. Smith:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); International Patent Application No. PCT/US25/47445.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.11/LL8

Topic: J.08. Methods to Modulate Neural Activity

Support: UH3NS103549

Title: Parameter Dependent Modulation of Pulse-Evoked Potentials During Deep Brain Stimulation

Authors: *A. ALIJANPOUROTAGHSARA[1], K. MIRPOUR[2], E. BARTOLI[4,8], S. RAJESH[2], S. CHILUKURI[2], A. GHAZAVI[2], R. MATHURA[11], G. WITTEN[2], E. TSOLAKI[12], N. R. PROVENZA[5,8,9,10], D. OSWALT[13], W. K. GOODMAN[6], S. A. SHETH[5,14,9,6,7], N. POURATIAN[2,3];
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Abstract: The efficacy of deep brain stimulation (DBS) depends on optimal modulation of stimulation parameters, yet how its two charge-determining parameters pulse width (PW) and current amplitude shape neural recruitment in the human brain remains poorly understood. Using pulse-evoked potentials (PEPs), the trial-averaged intracranial response to individual stimulation pulses, as a direct measure of recruitment, we tested whether PW and amplitude drive evoked responses through distinct, separable parameter-response functions rather than through total delivered charge alone. In a patient undergoing DBS for treatment-resistant depression, 8 DBS contacts (3 subcallosal cingulate, SCC; 5 ventral capsule/ventral striatum, VCVS) were stimulated across a PW (80-360 μs) and amplitude (3-9 mA) parameter space (253 conditions, 50 trials averaged each) while recording from 146 stereo-EEG channels. PEP magnitude (N1 and P1 prominence, peak amplitude, and area under the rectified response) was modeled per contact with linear mixed-effects models (FDR-corrected). Both PW and amplitude independently increased PEP magnitude across all contacts (PW: +5-56% per 100 μs; amplitude: +3-23% per mA; FDR<0.05), with dose-responses saturating when evaluated at fixed levels of the other parameter (negative quadratic term, FDR<0.05). Models including separate PW and amplitude terms outperformed charge-only models. At matched charge, amplitude evoked larger responses than PW (24/32 contact-by-outcome comparisons; median 1.4×), indicating separable effects beyond total delivered charge. Detection probability across channels increased with both PW (odds ratio 1.3-2.4 per 100 μs) and amplitude (1.2-1.7 per mA; FDR<0.05), indicating recruitment of additional sites. PW increased magnitude without altering latency. PW sensitivity differed by target, with stronger N1 modulation in SCC and stronger P1 modulation in VCVS (interaction $p<1\times10^{-13}$). Mixed-effects models predicted responses at withheld parameter settings (cross-validated R^2 up to 0.78) and generalized to a separately recorded session. Together, PW and amplitude produced separable, saturating effects on PEP magnitude and spatial recruitment while preserving latency. Their effects differed across targets and response components, with amplitude emerging as the more charge-efficient parameter. By quantifying how each parameter

shapes response magnitude, spatial extent, and target specificity, these parameter-response functions offer a principled basis for selecting stimulation settings and support PEPs as objective biomarkers of target engagement.

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Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.12/LL9

Topic: J.08. Methods to Modulate Neural Activity

Support: The Swebilius Foundation

Title: Rapid Multianalyte Quantification of Neurochemical Biomarkers Using Silicon-Nanoribbon Biosensors

Authors: *V. RAJAGOPALAN[1], J. MALDONADO[3], Y. GU[3], T. EID[2], D. D. SPENCER[4], H. P. ZAVERI[1];
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Abstract: Continuous real-time monitoring of chemical biomarkers is essential for advancing our understanding of neurological disorders and facilitating targeted therapeutic interventions. Conditions such as epilepsy involve disturbances in the excitatory-inhibitory balance of neural circuits, which are modulated by key neurochemicals including gamma-aminobutyric acid (GABA), lactate, and glutamate. Traditional detection techniques such as mass spectrometry or microdialysis lack the spatial specificity and temporal resolution required for research and clinical translation. Semiconductor field-effect transistor (FET)-based nanosensors represent an emerging solution, but their application has been limited due to inadequate real-time detection capabilities and inconsistent surface modification strategies. To address these shortcomings, we developed a complementary metal-oxide-semiconductor (CMOS)-based silicon nanoribbon FET biosensor capable of real-time, multiplexed, and label-free neurochemical detection. A versatile surface functionalization protocol was optimized, using monoclonal antibodies for GABA and

aptamer bioreceptors for lactate and glutamate. These sensors were validated in buffered solutions and artificial cerebrospinal fluid (aCSF). Real-time measurements achieved temporal resolution below 250 ms, and calibration curves were established for each neurochemical. The sensing platform enabled rapid neurochemical quantification within <10 minutes. Detection limits achieved were 80 fM for GABA, 58 fM for glutamate, and 182 fM for lactate. The sensors showed concentration-dependent responses, specificity against non-target molecules, and reliable performance in complex matrices such as aCSF. These results highlight the ability of this sensor to detect subtle shifts in inhibitory and excitatory neurochemicals, capturing physiologically relevant changes central to epileptogenesis and ictogenesis. This sensing platform addresses major limitations of existing neurochemical monitoring methods by enabling highly sensitive, selective, and rapid detection of GABA, lactate, and glutamate. The adaptable functionalization strategy supports multi-analyte detection in complex biological environments. These findings establish a strong foundation for integration with microdialysis systems and continuous in vivo monitoring of brain chemistry. Such capabilities may improve diagnostic accuracy and therapeutic efficacy in epilepsy care and prove useful for other neurological and neuropsychiatric disorders requiring sensitive real-time biochemical measurement.

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Poster

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Program #/Poster #: PSTR118.13/LL10

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01-NS133229.

Title: Temporal Interference Stimulation Affects Visual Perception in a Stimulus-Onset Asynchrony Task in Non-Human Primates

Authors: *J. GODBOUT[1], K. TSUNODA[2], T. WEBB[3], S. RAMPERSAD[5], M. YAROSSI[6], A. D. DORVAL[2], J. KUBANEK[4];
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Abstract: Temporal interference stimulation (TIS) is an emerging noninvasive neuromodulation technique designed to target deep brain circuits. Conventional transcranial neuromodulation modalities - e.g., alternating current (tACS), direct current (tDCS), and magnetic (tMS) stimulation - share a common fundamental limitation: a trade-off between brain penetration depth and neural activation focality. The TIS approach has the potential to circumvent this limitation, leveraging two "carrier" frequencies offset by a small frequency difference, TIS can

generate a neuromodulatory "beat" within deep brain structures. This approach may enable focal targeting of deep brain structures without activating off-target regions, e.g., in the overlying cortex. Establishing the precise stimulation parameters for efficacious TIS is critical for its eventual utilization in clinical applications. We employed TIS to investigate visual bias modulation in rhesus macaques using a stimulus-onset asynchrony (SOA) task. This behavioral paradigm assessed the specific effects of TIS targeted on the lateral geniculate nucleus (LGN). In head-fixed subjects, gaze was continuously monitored using an EyeLink infrared eye tracker (SR Research). Stimulation was delivered via the Real-Time eXperiment Interface (RTXI) system, which generated two independent electrical signals, amplified by linear isolators, and transmitted via implanted cranial screws. The stimulation paradigm utilized a 1000 Hz carrier frequency, with beat frequencies of 2.5, 5, 10, 20, and 40 Hz to probe different neural entrainment effects. Amplitude modulation was applied at 90% (1.75 mA: 1.575 mA), 80% (1.75 mA: 1.4 mA), and 60% (1.75 mA: 1.05 mA) ratios to spatially refine LGN targeting. A sham condition, in which identical carrier frequencies (0 Hz beat frequency) were delivered bilaterally, served as a control for non-beat stimulation artifacts. This study employed a sigmoidal psychometric function to analyze leftward choice behavior, with percentage values assigned to each delay condition. Under ideal circumstances, a 0 ms delay would be expected to yield a 50% success rate, reflecting chance-level performance. For data analysis, the recorded baseline value at which the psychometric curve crossed the 50% likelihood threshold was used as a comparison point between parameter setups. The 5 Hz beat frequency showed an approximately 15% greater biasing effect on average compared to the sham and pre-trial baseline. The remaining beat frequencies did not exhibit similar behavior and therefore did not show comparable evidence of visual-bias modulation, supporting further optimization of key TIS parameters

Disclosures: J. Godbout: None. **K. Tsunoda:** None. **T. Webb:** None. **S. Rampersad:** None. **M. Yarossi:** None. **A.D. Dorval:** None. **J. Kubanek:** None.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.14/LL11

Topic: J.08. Methods to Modulate Neural Activity

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The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, in the amount of ($258 606), through the Peer Reviewed Medical Research Program under Award No. HT9425-24-1-0018

Title: Transnasal electrical stimulation (TnES) of the deep brain in an in vivo mouse model

Authors: *Y. LEE[1], V. JAIN[2], P. GROVER[3], M. FORSSELL[2];
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Abstract: Therapeutic deep brain stimulation is being investigated for various neural disorders, but its adoption is limited by surgical implantation carrying infection risks and high costs. Transnasal electrical stimulation (TnES) is a minimally-invasive approach to stimulate the deep brain through nasal cavities. Previous computational and cadaveric studies in a human model indicated that TnES generates focal electric fields in the deep brain. In this study, we developed a TnES platform for an in vivo mouse model. Following anesthesia with ketamine/xylazine cocktail, a linear 32-electrode probe (50μm diameter at 100μm pitch) was positioned in the nasal pathway below the hypothalamus (HT). A 64-electrodes recording probe, coated with DiI stain for post-hoc histological tracing, was inserted into the brain targeting the HT. Electrical stimulation was applied through two electrodes in the nasal probe which were separated by 3.1 mm. Following stimulation using 3-6 mA biphasic pulses (500 μs/pulse, 10 pulses), brains were extracted, fixed in 4% PFA, and sectioned with 100 μm thickness (Fig (A)). Histological probe tracing defined depth boundaries for the cortex (CX), hippocampus (HP), dorsal thalamus (DT), ventral thalamus (VT), and HT. Fig (B) shows pre- and post-stimulus electrophysiological signals of DT, VT, and HT. Fig (C) presents temporal dynamics (% changes in root-mean-square (ΔRMS)) of neural signals in 10-ms bins over [-100, 250] ms. In HT, DT, HP, maximal responses occurred early (<10 ms), and ΔRMS increased as the applied current was increased from 3 to 6 mA (2.3✕ in HT, 2.9✕ in DT, 1.5✕ in HP). In VT and CX max ΔRMS were delayed >20 ms. In addition, the max ΔRMS in VT and CX values are between 234% and 248% and between 273% and 280%, whose variances are small despite the applied current being high. Out of two, one animal showed responses in HP at 60 ms (6 mA). Signal recovery to baseline occurred at approximately 100 ms for HP and CX, and 200 ms for VT. Prominent responses persisted beyond 250 ms in DT and HT. Using the in vivo TnES setup developed, neural responses were observed in multiple brain areas.

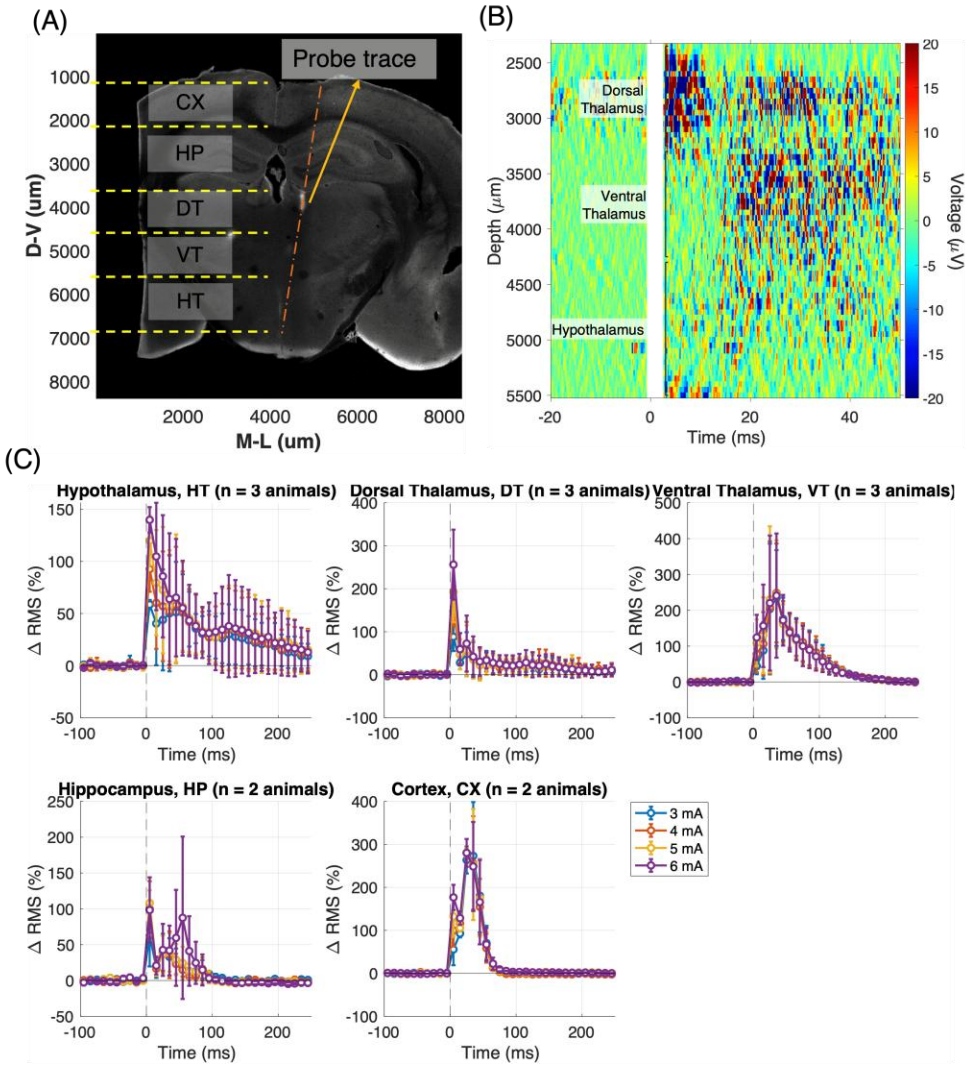


Fig. (A) Post-hoc histological probe tracing in a brain slice. The orange line indicates a probe trajectory across multiple brain slices. The fluorescent stain (DiI stain) trace of the brain slice is shown in DT. Based on the thickness of the brain slices and the pixel size of the images, the estimated boundaries of the brain structure were determined. (B) Electrophysiological signals (one animal, one pulse) of deep brain areas (HT, VT, DT) before and after stimulation (stimulation onset at 0 ms). The boundaries between brain regions were determined based on the probe trace (A). Spontaneous responses (pre-stimulation) are observed in DT. The characteristics of evoked signals are different across brain areas. (C) Temporal neurodynamics across different brain regions (HT, VT, DT, HP, CX). Post-stimulus responses were normalized as a percentage change (ΔRMS) relative to the pre-stimulus baseline (averaged from -100 to 0 ms). Within each animal, responses were averaged across 10 pulses, and group-level mean and standard deviation were then calculated from the normalized ΔRMS values.

Disclosures: Y. Lee: None. **V. Jain:** None. **P. Grover:** None. **M. Forssell:** None.

Poster

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Program #/Poster #: PSTR118.15/LL12

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant R01 NS138733
NIH Grant S10 OD021773
NIH Grant R01 NS129984
NIH Grant R21 NS132071

Title: Focality of temporal interference electrical stimulation assessed in mouse models at single-cell levels

Authors: R. YOSHIMOTO, M. A. STERN, B. BARNES, C.-A. N. GUTEKUNST, ***K. BERGLUND**;
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Abstract: Temporal interference (TI) electrical stimulation is an emerging approach for noninvasive deep brain neuromodulation. It has been believed that neurons selectively respond to the low-frequency envelope generated in the deep brain by the interaction of two high-frequency currents applied at the surface of the brain while they remain largely insensitive to the high-frequency stimulation itself. The spatiotemporal focality and the working principles of TI remain poorly understood. We therefore conducted *ex vivo* and *in vivo* two-photon fluorescence microscopy in mice expressing an indicator protein for calcium or voltage. Additionally, we conducted computational modeling of TI stimulation.

Contrary to the conventional assumption, high-frequency stimulation alone evoked neuronal responses, demonstrating that carrier frequency is not physiologically inert. In contrast to sustained activity during high-frequency stimulation, the addition of amplitude modulation caused rhythmic activity at the beat frequency. Power spectral density increased at the beat frequency as the degree of amplitude modulation increased. During TI stimulation, responding neurons were broadly distributed across the imaging field, indicating that neuronal recruitment was not restricted to the focus of TI. Rhythmic entrainment was strongest near the center of interference, revealing a distinct pattern of activity and synchronicity. Similar findings were observed *in vivo* in anesthetized mice, where TI stimulation induced neuronal activity entrained at the beat frequency while carrier-only stimulation elicited responses lacking clear rhythmic structure. Using current amplitudes insufficient to evoke action potentials, voltage imaging in brain slices revealed rhythmic depolarization during TI stimulation. Calcium imaging *in vivo* in awake mice similarly confirmed that TI stimulation with equivalent amplitudes produced oscillatory modulation. Computational modeling suggested that differential temporal dynamics between sodium and potassium channels contribute to the responses to high-frequency stimulation. Our model predicted that neuronal compartments with high density of sodium channels are the most susceptible to TI.

Taken together, our study revealed spatiotemporal patterns of neuronal activity during TI stimulation at the spatial resolution of single-cell levels. Our findings challenge the conventional

assumption that neurons are largely unresponsive to unmodulated high-frequency stimulation and suggest, instead, that focality of TI arises primarily through localized temporal entrainment at the interference locus.

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Poster

PSTR118: Electrical

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Program #/Poster #: PSTR118.16/LL13

Topic: J.08. Methods to Modulate Neural Activity

Support: UG3NS123723

Title: A Translational Platform for Precise Spinal Cord Neuromodulation

Authors: *F. KHOURY[1], E. SINOPOULOU[4], R. VATSYAYAN[5], S. FISHER[2], J. LEE[3], W. JEON[1], K. LEE[6], M. H. TUSZYNSKI[8], S. DAYEH[7];
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Abstract: Spinal cord injury (SCI) is a devastating neurological condition that results in the loss of motor, sensory, and autonomic function. Current therapeutic rarely restore lost neural circuitry because of the spinal cord's limited intrinsic regenerative capacity. Recent advances in neuromodulation have demonstrated that epidural spinal cord stimulation (EES) can re-engage spinal networks and restore voluntary movement or standing ability in individuals with clinically complete SCI by increasing the excitability of spinal circuitry and enabling integration of residual supraspinal inputs. Clinical studies combining EES with activity-based rehabilitation have shown that individuals with chronic cervical SCI can achieve independent lower-limb extension and weight-bearing standing during stimulation training. In parallel, neural stem cell (NSC) transplantation has emerged as a promising regenerative strategy capable of replacing lost neurons and glia, remyelinating axons, secreting trophic factors, and forming relay circuits that reconnect disrupted pathways. Here, we hypothesize that combining high-resolution epidural stimulation with neural stem cell transplantation can synergistically enhance functional recovery after SCI. To enable this strategy, we developed high-channel-count thin-film epidural microelectrode arrays that can be tailored to the spinal anatomy and deliver spatially selective stimulation using adaptive charge modulation, enabling improved focal activation of spinal circuits. In a healthy rat model, high-density stimulation produced focal and controlled motor

recruitment, enabling reliable grasping motions that highlight the spatial precision achievable with this technology. In a rat model of SCI, these devices demonstrated stable electrode impedance for up to 68 days following implantation. Building on these results, we are developing MRI-informed wireless spinal implants for non-human primate studies, targeting a C5 spinal cord injury model combined with human-derived neural stem cell transplantation. In parallel, we are evaluating these cleanroom-manufactured electrode platforms in accelerated aging systems to assess long-term device reliability, including the integration of ceramic encapsulation within thin-film implants to support chronic implantation and address the longstanding limitations of polymer-based implants in stability and longevity. Together, this combinatorial neurotechnology platform aims to restore functional motor control after spinal cord injury and represents a promising step toward clinically scalable therapies.

Disclosures: F. Khoury: None. **E. Sinopoulou:** None. **R. Vatsyayan:** None. **S. Fisher:** None. **J. Lee:** None. **W. Jeon:** None. **K. Lee:** None. **M.H. Tuszynski:** None. **S. Dayeh:** None.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

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Program #/Poster #: PSTR118.17/LL14

Topic: J.08. Methods to Modulate Neural Activity

Title: Intracellular recording and modulation enabled by CMOS electrode array

Authors: *J. WANG;
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Abstract: Electrodes have long provided a window into neuronal activity and network dynamics. Patch-clamp electrodes offer intracellular access with sufficient sensitivity to measure subthreshold synaptic signals, but are limited to one or a few neurons at a time. In contrast, microelectrode arrays (MEAs) enable parallel recording from large neuronal populations, but are generally restricted to extracellular measurements and lack sensitivity to intracellular events. Achieving patch-clamp-like intracellular access with MEA-like scalability has remained a longstanding challenge. Here, we report a 4,096-channel CMOS microhole electrode array that enables parallel intracellular recording from thousands of neurons through controlled pA-nA current injection. By optimizing the current injection protocol, the membrane perturbation was reduced, which enables intracellular re-access to the same neuronal population, and improved recording stability. The platform also supports single-cell-resolution neuronal modulation through the same electrode array. Using simultaneous intracellular recordings across large neuronal populations, we demonstrate the capability for network-scale analysis of neuronal interactions and synaptic connectivity. Furthermore, the combination of intracellular recording and targeted modulation provides a powerful tool for investigating synaptic plasticity. These results establish CMOS microhole electrode arrays as a scalable platform for high-throughput intracellular electrophysiology and bidirectional neural interfacing.

Disclosures: J. Wang: None.

Poster

PSTR118: Electrical

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Program #/Poster #: PSTR118.18/LL15

Topic: J.08. Methods to Modulate Neural Activity

Support: R01 NS125435

Title: An open, hard-real-time, sub-3 ms platform for closed-loop neural control with online learning

Authors: *W. A. WALKER, J. T. FRANCIS;
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Abstract: Closed-loop neuromodulation is already possible, but most current systems use relatively simple control strategies. Research systems often rely on threshold rules or basic feedback controllers, while clinical devices usually use fixed, pre-set stimulation policies.
We introduce an open platform that allows researchers to build and modify their own closed-loop controllers. Instead of delivering fixed stimulation settings, the system updates stimulation on every cycle based on the brain activity it is recording at that moment. It uses a predictive model to decide how stimulation should change, and that model can continue learning during the experiment.
The platform runs on Intan's commercial RHS hardware, supporting 128 channels in a plug-and-play setup. Our custom software can update stimulation settings on every channel while recording is still ongoing. The controller is written in Python and runs on a GPU, while a second computer retrains the model in real time and can replace it with an improved version during the experiment without stopping the loop.
On a hard-real-time computer, the time from recording brain activity to updating stimulation is under 2 ms, and a compact controller can complete the full closed-loop cycle in under 3 ms. As a demonstration, we implemented a deep Koopman model predictive controller and validated the full system in vivo.

Disclosures: W.A. Walker: None. **J.T. Francis:** None.

Poster

PSTR118: Electrical

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Program #/Poster #: PSTR118.19/LL16

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH grant FAIN U01NS131086

Title: A high-density bidirectional neural interface enabled by integration of ultraflexible probes with a 512-channel ASIC

Authors: ***W. WANG**[1], P. ZOLOTAVIN[2], C. XIE[2], T. CHI[2], X. ZHANG[2], L. LUAN[2];
[1]Rice Univ., HOUSTON, TX; [2]Rice Univ., Houston, TX

Abstract: Penetrating neural probes have enabled extracellular recordings from neuronal populations with single-unit resolution and millisecond temporal precision. Scaling these interfaces is important for mapping distributed brain dynamics and for brain-computer interfaces, where larger and more stable neural populations can support richer decoding and feedback. High-density silicon probes such as Neuropixels have transformed systems neuroscience by providing dense, scalable recordings across local circuits and multiple brain regions. However, most high-channel-count penetrating probes are optimized primarily for recording. Because electrode geometry, implant mechanics, and front-end electronics are often tightly coupled, it remains challenging to combine large-scale single-unit recording with flexible probe designs, chronic tissue compliance, and freely configurable, multi-site electrical stimulation.
Here, we present a modular 512-channel bidirectional neural interface integrating an ultraflexible e-beam-lithographed neural probe with a custom application-specific integrated circuit (ASIC). The ASIC supports simultaneous recording from 512 channels and stimulation from up to 128 channels. The probe uses dense e-beam-defined interconnects to route each electrode to an independent trace, increasing channel count within a small implantation footprint while preserving the mechanical compliance of an ultraflexible substrate. This one-electrode-one-trace architecture enables recording and stimulation across arbitrary combinations of contacts, including recording and stimulation on the same contact with submillisecond switching.
The integrated probe-ASIC design further supports freely configurable patterned stimulation, with microsecond-scale control of waveform timing and programmable combinations of stimulation channels during simultaneous recording. We validated the assemblies through in vitro electrical characterization and in vivo neural interfacing. The system recorded neuronal spiking activity at single-unit resolution across hundreds of channels and maintained functional performance over months after implantation. Together, these results establish a scalable bidirectional neural interface that combines high-density ultraflexible probes, custom integrated electronics, and programmable multi-contact stimulation for chronic, large-scale interrogation of neural circuits.

Disclosures: W. Wang: None. **P. Zolotavin:** None. **C. Xie:** None. **T. Chi:** None. **X. Zhang:** None. **L. Luan:** None.

Poster

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Program #/Poster #: PSTR118.20/LL17

Topic: J.08. Methods to Modulate Neural Activity

Support: R01 NS119390/NS/NINDS NIH Grant

Title: Characterizing Neural Activation Patterns Following Afferent-Selective Vagus Nerve Stimulation

Authors: *D. NGUYEN[1], S. KHAN[2], A. ALEXANDRIS[3], V. E. KOLIATSOS[4];
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Abstract: Electrical vagus nerve stimulation (VNS) is an established neuromodulation therapy whose clinical effects likely involve both afferent and efferent vagal pathways, though the relative contributions of each remain undetermined. Afferent-selective electrical VNS has emerged as a means of isolating vagal sensory signaling, yet its effects on neural circuits remain largely unexplored. We hypothesized that eliminating VNS-evoked efferent recruitment would alter the magnitude and distribution of VNS-induced neural activation, revealing nuclei preferentially associated with afferent signaling. Here, we sought to characterize neural activation patterns induced by afferent-selective electrical VNS and compare them with those produced by conventional VNS. Adult rats received conventional VNS, afferent-selective VNS, or sham stimulation. Afferent selectivity was validated using laryngeal electromyography (efferent) and c-Fos expression in the nucleus tractus solitarius (NTS, afferent). Activation of multiple downstream brainstem nuclei was characterized, including the parabrachial nucleus, locus coeruleus, dorsal raphe nucleus, ventral respiratory group, nucleus ambiguus, nucleus retroambigualis, area postrema, dorsal motor nucleus of the vagus, and spinal trigeminal nucleus. Afferent-selective VNS completely eliminated stimulation-evoked laryngeal activity observed during conventional VNS (ANOVA, $p = 0.0288$; Sidak post hoc, $p = 0.0331$), with responses indistinguishable from sham controls ($p = 0.9997$), confirming suppression of efferent fibers. Despite elimination of efferent motor activation, both conventional VNS and afferent-selective VNS induced significant ipsilateral NTS c-Fos expression, with mixed-effects analysis demonstrating significant effects of group ($p = 0.0170$), laterality ($p = 0.0002$), and group × laterality interaction ($p = 0.0073$). Quantification of downstream brainstem nuclei is ongoing and will be presented. These findings establish a framework for determining how selective, electrical stimulation of vagal afferents impacts neural activity, contributing to its therapeutic effects.

Disclosures: D. Nguyen: None. **S. Khan:** None. **A. Alexandris:** A. Employment/Salary (full or part-time):; Johns Hopkins School of Medicine. **V.E. Koliatsos:** A. Employment/Salary (full or part-time):; Johns Hopkins School of Medicine.

Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.21/LL18

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH NINDS NS102917

Title: Maximizing Information Encoding by Bottom-Up Construction of Patterned Intracortical Microstimulation with High-Density Ultraflexible Electrodes

Authors: *Y. LIU[1], R. J. LYCKE[1], X. ZHANG[1], R. KIM[1], P. ZOLOTAVIN[1], N. P. SHAH[2], L. LUAN[2], C. XIE[2];
[1]Rice Neuroengineering Initiative, [2]Electrical and Comptuer Engin., Rice Univ., Houston, TX

Abstract: Maximizing Information Encoding by Bottom-Up Construction of Patterned Intracortical Microstimulation with High-Density Ultraflexible Electrodes
Authors: Yuxuan Liu*, Roy Lycke, Xiaorong Zhang, Robin Kim, Pavlo Zolotavin, Nishal Shah, Lan Luan, Chong Xie**
Neural representations are encoded in high-dimensional population activity, yet current intracortical microstimulation (ICMS) approaches remain limited in their ability to impose neural activity patterns with comparable complexity. This limitation reflects both an incomplete mechanistic understanding on how neural populations respond to spatiotemporally patterned electrical stimulation and the lack of quantitative frameworks for evaluating how stimulation parameters shape information-bearing population responses. Here, we developed a bottom-up strategy for constructing patterned ICMS using high-density ultraflexible electrodes, combined with two-photon calcium imaging and simultaneous electrical recording to measure the resulting populational activity.We first defined a set of elementary ICMS “building blocks”, and tested how their combinations shaped evoked neural activity. Combined stimulation patterns increased the diversity of population responses, and the resulting activity could not be trivially explained by linear superposition of single-block responses, indicating substantial nonlinear interactions with the ICMS mechanism and the stimulated circuit. We then generated families of stimulation patterns across a range of delivered charge rates and quantified the information encoded of evoked population responses using pairwise correlation-based population metrics. This analysis revealed the relationship between delivered charge rate and per-neuron information estimate, suggesting an optimal stimulation regime for maximizing population-level encoding. Within this regime, distributing charge across more stimulation sites generally produced more diverse and discriminable neural responses.Finally, we compared electrically evoked population trajectories with visually evoked activity elicited by simple stimuli, including drifting gratings. Optimized ICMS patterns occupied a broad region of low-dimensional neural state space and partially overlapped with visually evoked manifolds, with response consistency approaching that of visual stimulation. Together, these results establish a quantitative bottom-up framework for constructing patterned ICMS and provide a foundation for future cortical visual prostheses that aim to reproduce sensory-evoked population activity rather than sparse phosphene maps alone.

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Poster

PSTR118: Electrical

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 1:00 PM - 5:00 PM

Program #/Poster #: PSTR118.22/LL19

Topic: J.08. Methods to Modulate Neural Activity

Title: A Mathematical Model of Norepinephrine Release Dynamics in Response to Vagus Nerve Stimulation

Authors: *P. ZARE[1], E. MEYERS[1], S. A. HAYS[2], M. P. KILGARD[3];
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Abstract: Pairing vagus nerve stimulation (VNS) with rehabilitation enhances recovery in chronic stroke and other neurological disorders, yet many individuals fail to benefit, highlighting the need to optimize stimulation parameters. VNS-dependent plasticity is governed by noradrenergic signaling, but the complex relationship between stimulation parameters and plasticity magnitude has hindered systematic optimization.To comprehensively characterize this relationship, rats underwent five days of training on a behavioral task in which VNS at varying parameters was paired with jaw movement during chewing. Stimulation intensity (0.5-3.2 mA), frequency (30-120 Hz), and pulse number (1-64 pulses) were systematically varied across a wide parameter space. Cortical plasticity was assessed the following day using intracortical microstimulation (ICMS) of the motor cortex.Based on these experimental results, we developed a mathematical model that predicts norepinephrine levels as a function of VNS electrical parameters. The model defines an optimal norepinephrine range, bounded by α- and β-adrenergic receptor activation thresholds, within which stimulation parameters enhance plasticity. Parameters producing norepinephrine levels outside this range — reflecting either insufficient or excessive noradrenergic activation — fail to drive plasticity, confirming the inhibitory effects of noradrenergic overactivation. Model predictions were validated against experimental outcomes across the full range of stimulation parameters tested in vivo.These findings establish a mechanistically driven, rational framework for selecting VNS parameters that maximize cortical plasticity, offering a direct translational pathway to meaningfully enhance the clinical efficacy of VNS therapy.

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Poster

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Program #/Poster #: PSTR118.23/LL20

Topic: J.08. Methods to Modulate Neural Activity

Support: UG3NS131971
Blueprint MedTech Optimizer

Title: Implanted Vagus Nerve Stimulation Produces Distinct Neural and Physiological Responses Compared with Auricular Nerve and Cutaneous Stimulation

Authors: *Z. S. BYNUM[1,2], A. M. BOLLINGER[1,3], S. A. HAYS[1,3], E. C. MEYERS[1,3], M. P. KILGARD[1,2];
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Abstract: Implanted vagus nerve stimulation (iVNS) has been shown to improve the benefits of rehabilitation in preclinical models and in individuals with spinal cord injury (SCI) and stroke. Auricular nerve stimulation has emerged as a non-invasive neuromodulatory alternative by stimulating the cymba, but results are inconsistent. The acute neural and physiological signatures of vagal engagement during iVNS remain poorly understood, and it is unclear whether auricular nerve stimulation produces similar responses to iVNS or more closely resembles cutaneous stimulation. This study compares acute biomarkers of central and autonomic function through continuous non-invasive physiological monitoring in healthy adults and individuals with SCI and stroke. Participants underwent randomized, interleaved, phasic stimulation of the vagus nerve, earlobe, cymba, and fingertip while electroencephalography (EEG), electrocardiography (ECG), respiration, galvanic skin response (GSR), pupillometry, and laryngeal electromyography (LEMG) were recorded during resting state observation. Healthy adults received cymba, earlobe, and fingertip stimulation while individuals with SCI and stroke received iVNS and cymba stimulation. Across healthy adults (n=37), stimulation of the cymba, earlobe, and fingertip elicited indistinguishable changes in pupil dilation amplitude, pupil dilation latency, respiration, ECG morphology, heart rate variability, or LEMG. In a subset of healthy adults (n=12), stimulation of the cymba, earlobe, and fingertip elicited indistinguishable somatosensory evoked potentials. In individuals with SCI and stroke (n=5), iVNS produced subject specific pupil, EEG, and LEMG responses while no consistent responses were observed in ECG, respiration, or GSR. These findings suggest that cymba, earlobe, and fingertip stimulation evoke equivalent arousal responses, likely through cutaneous response. Ongoing studies in iVNS populations will characterize potential biomarkers of vagal engagement that could support development of personalized stimulation strategies to optimize therapeutic outcomes.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH/NIBIB P41EB018783
SPiRE 5I21RX004410-02
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Stratton VA Medical Center

Title: Closed-loop vagus nerve stimulation as a reinforcement signal for h-reflex operant conditioning

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Abstract: Spasticity after stroke and spinal cord injury is a major driver of disability, yet effective treatments that selectively target spinal reflex circuits underlying spasticity remain limited. H-reflex (HR) operant conditioning (HROC) reduces reflex excitability by delivering a reinforcement when HR amplitude falls below criterion. Pre-clinical studies demonstrate successful reflex modulation, and early clinical trials suggest functional improvement. However, HROC's reliance on explicit, attention-demanding reinforcement over prolonged training timelines (8 weeks of 24/7 conditioning pre-clinically; 1-hour sessions, 3x week for 12 weeks clinically) may exclude individuals unable to sustain prolonged cognitive engagement and limit translational scalability. Vagus nerve stimulation (VNS), delivered closed-loop with training events, engages locus coeruleus-noradrenergic and raphe-serotonergic projections to the spinal cord, delivering a timed neuromodulatory signal to the spinal circuits underlying HR amplitude — the same circuits targeted by conventional food-reinforced HROC. In our V-HROC paradigm, successful down-conditioning trials (defined as HR amplitude falling below the 30th percentile of each rat's HR size distribution) receive VNS reinforcement. We hypothesize that VNS delivered following successful conditioning trials can substitute for food-pellet reward reinforcement by serving as a neuromodulatory reinforcement signal, producing HR down-conditioning comparable to food-reinforced HROC. Adult female Sprague-Dawley rats chronically implanted with vagus and tibial nerve stimulating cuffs undergo HROC, in which HRs are elicited via tibial nerve stimulation and soleus responses are captured from bipolar implanted EMG electrodes. Down-conditioning trials determined to be successful receive either: (1) VNS; (2) standard food pellet reward; or (3) no reinforcement (no VNS or food-pellet). This design allows us to assess how reinforcement modality shapes HR plasticity; the no-reward group confirms that HR changes in the CNV group are driven by VNS acting as a reward, not by VNS stimulation alone suppressing the reflex. Primary outcomes are rate of down-conditioning (time to reach target reduction) and magnitude of suppression (total reduction in reflex amplitude); group comparisons assess whether VNS can substitute for food reinforcement in driving HR plasticity. These experiments test whether VNS-mediated neuromodulatory reinforcement is sufficient to drive spinal operant plasticity, providing a mechanistic foundation for attention-independent HROC protocols targeting hyperreflexia and spasticity.

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Poster

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH NINDS Blueprint MedTech Optimizer U54EB033664

Title: Electromyography Based Movement Decoding for Delivery of Closed Loop Vagus Nerve Stimulation

Authors: *R. SWITZER[1,2], S. GOPALAKRISHNAN[1], F. TASKIN[3], S. A. HAYS[1,2], M. P. KILGARD[1,4], H. CHANG[3], R. L. RENNAKER[1,4], D. FRIEDENBERG[5], E. MEYERS[1,2]; [1]Texas Biomed. Device Ctr., [2]Bioengineering, [3]Natural Sci. and Mathematics, [4]Behavioral and Brian Sci., The Univ. of Texas at Dallas, Richardson, TX; [5]Hlth. Analytics, Battelle Mem. Inst., Worthington, OH

Abstract: Closed-loop vagus nerve stimulation (CLV) has emerged as a promising adjuvant to traditional physical and occupational therapy for the recovery of motor function following neurological injuries such as stroke and spinal cord injury. CLV elicits the release of neuromodulators throughout the brain, which is thought to transiently increase neuroplasticity of relevant neural circuits. Consequently, CLV has been shown to be most effective when stimulation is paired precisely with targeted high-quality movements. Our previous clinical trials have utilized inertial measurement units (IMU) to pair stimulations; however, IMU-based triggering requires sufficiently large movement and is unable to pair stimulation if limited or no residual movement exists. Additionally, this approach is reliant on simple, predefined exercises to ensure that sensors pick up the intended movements. To address these limitations, this study investigates the use of high-definition surface electromyography (HD-EMG) as an approach for pairing CLV with targeted movements. Using a novel HD-EMG device containing 30 electrodes worn over the wrist and forearm, this study aims to develop machine learning based approaches for decoding target movements from patterns of muscle activation. HD-EMG data from the paretic limb of individuals with chronic upper limb motor deficits following stroke has been collected. During sessions, participants donned the HD-EMG device and were led through a series of computer-guided isometric movements, including digit extension, digit flexion, wrist extension, wrist flexion, pronation, and supination, while EMG was recorded. Individual machine learning models were trained to decode either individual target movements or all movements. In subsequent sessions, pre-trained decoders were used during simulated activities of daily living to evaluate real-world decoding performance on complex movements. Preliminary results show that decoding models can achieve high levels of accuracy across both specific movement models (Ave. Accuracy 93% ± 9% SEM) and all movement models (Ave. Accuracy 85% ± 10% SEM). Model accuracy declines with higher levels of impairment; however, accuracy remained higher than chance even in cases where little to no movement existed, reinforcing the idea that EMG-based CLV may allow for paired stimulation even when this lack of movement would render IMU-based triggering impractical. These results demonstrate the

feasibility of using HD-EMG decoding for the pairing of CLV precisely with more complex movements, and, potentially, outside of structured therapy sessions.

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Poster

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Program #/Poster #: PSTR118.26/LL23

Topic: J.08. Methods to Modulate Neural Activity

Support: CDMRP
HT94252310818

Title: Preliminary Data: Randomized Controlled Trial of Vagus Nerve Stimulation for Treatment-Resistant Posttraumatic Stress Disorder

Authors: *J. P. VALENCIA[1], S. SODIMU[1], R. RAHMAN[1], J. SMITS[5], M. POWERS[2], R. L. RENNAKER[1,6], J. WIGGINTON[3,6], S. A. HAYS[4,6], M. P. KILGARD[1,6];
[1]Neurosci., [3]Clin. and Translational Res. Ctr., [4]Bioengineering, [2]Univ. of Texas at Dallas, Richardson, TX; [5]Univ. of Texas, Austin, TX; [6]Texas Biomed. Device Ctr., Richardson, TX

Abstract: Posttraumatic Stress Disorder (PTSD) is a psychiatric disorder impacting about 12 million adults in the US each year. The most effective treatment for PTSD is exposure-based therapy, such as Prolonged Exposure (PE). Although exposure-based therapies are the gold-standard treatment for PTSD, 18% of individuals seeking treatment drop out, more than 50% of individuals who complete therapy do not improve, and 67% do not achieve complete remission. This demonstrates a need for improving the tolerability and effectiveness of exposure-based therapies. Vagus nerve stimulation (VNS) may be a potential adjuvant to therapy for treatment-resistant PTSD by enhancing extinction learning and improving the tolerability of therapy. VNS is delivered during therapy sessions to trigger release of neuromodulators that promote synaptic plasticity in engaged brain networks and concurrently activate the parasympathetic nervous system. A previous open-label study investigating VNS paired with PE in a treatment-resistant PTSD population showed a complete loss of PTSD diagnosis at 1, 3, and 6 months post-therapy across 7 participants. To further validate these findings, this study aims to implement a double-blind, randomized placebo-controlled trial to investigate VNS paired with PE in 20 participants with treatment-resistant PTSD. This trial serves as the 2nd feasibility study of a novel-miniaturized VNS device and expands on the previous open-label study's limitations by

including a control group, double-blinding, randomization, and a projected sample size of 20. In Phase 1, participants will be blinded and randomly assigned to either the active VNS or sham VNS group for 12 PE sessions. Phase 2 serves as an open-label extension (OLE) for all participants, allowing them to receive VNS for an additional 12 PE sessions, as needed. Assessments measuring trauma-related memory processing and stress will be administered prior to implantation, at the end of Phase 1, 1 month after the end of Phase 1, at the end of Phase 2, and 1 and 6 months after the completion of Phase 2. Currently, 9 participants have completed therapy with no serious or unexpected device-related adverse events. Due to double blinding measures, comparisons cannot be made between the Immediate Start VNS group and Delayed Start VNS group. However, from consolidating all participants preliminary data before therapy and 1 month following their last therapy visit, a paired samples t-test indicated significantly lower PTSD severity following therapy, $t(8) = 8.46$, $p < .001$. This trial will provide robust evidence on the safety and efficacy of VNS as a potential adjuvant to therapy. Projected study completion is 06-2028

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Poster

PSTR118: Electrical

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Program #/Poster #: PSTR118.27/LL24

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

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Title: Metal Organic Framework Modified Multielectrode Arrays for Enhanced Neuropeptide and Neurochemical Detection

Authors: *A. G. C. ZESTOS;
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Abstract: Carbon fiber microelectrodes (CFMEs) have been used to detect neurotransmitters and other biomolecules using fast-scan cyclic voltammetry (FSCV) for the past few decades. These assays typically measure small molecule neurotransmitters such as dopamine and serotonin. The carbon fiber is relatively small, biocompatible, and makes minimally invasive measurements at high spatial and temporal resolution. CFME arrays have been utilized to measure multiple neurotransmitters in several brain regions simultaneously with multi-waveform application on each electrode. We have extended this work to measure larger molecule

neuropeptides such as endorphins, galanin, Neuropeptide, Y and Oxytocin, a pleiotropic peptide hormone, which is physiologically important for adaptation, development, reproduction, and social behavior. This neuropeptide functions as a stress-coping molecule, an anti-inflammatory agent, and serves as an antioxidant with protective effects especially during adversity or trauma. Here, we measure tyrosine using the Modified Sawhorse Waveform (MSW), enabling enhanced electrode sensitivity for the amino acid and peptide, decreased surface fouling, and codetection with other catecholamines. Endorphins are three proteins that belong to a family of neuropeptides that regulate pain perception, mood, and immune function by targeting opioid receptors. The biological role of β-endorphin is well studied, but α- and γ-endorphin are less understood. By creating more fast and reliable methods of detection, we can progress towards determining the physiological role of each endorphin. Using enzymatic modifications to CFMEs such as glutamate oxidase, we have also been able to measure non-redox active amino acids within peptide chains such as glutamate to enhance sensitivity and selectivity. By developing novel electrochemical sensors and tools for peptide analysis, we hope further analyze these compounds and determine their physiological roles *in vivo*. In order to enhance neurochemical and neuropeptide detection with FSCV, we will modify CFMEs with the iron-based metal-organic framework MIL-88B(Fe) MOF to increase surface area and catalytic adsorption sites for neurochemical detection.

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