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Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.01/D20

Topic: A.06. Developmental Disorders

Title: 3D open field: Varied topography enhances detection of motor phenotypes in a mouse model of Angelman syndrome

Authors: *J. J. SHIDE[1], C. D. GUOYNES[2], D. MONTGOMERY[3], S. BETTS MENDIZABAL[4], M. S. SIDOROV[5];
[2]Psychology, [3]Ctr. for Neurosci. Res., [1]Children's Natl. Hosp., Washington, DC; [4]George Washington Univ., Washington, DC; [5]Ctr. for Neurosci. Res., Children's Natl. Med. Ctr., Washington, DC

Abstract: Ongoing clinical trials for Angelman syndrome (AS) rely on behavioral assays to gauge treatment response in model animals. However, existing assays often collapse behavior into summary metrics, potentially obscuring subtler behavioral phenotypes. Our lab sought to address this limitation by developing the 3D open field: a novel variant of the open field test incorporating modular 3D-printed blocks of varying heights. By altering the configuration of these blocks, we can shape the occurrence of specific behaviors, and by analyzing transitions between blocks, we can evaluate patterns of exploratory motor behavior. Additionally, through the application of Keypoint MoSeq, an automated behavioral classification software, we can assess phenotypic differences at the level of individual transition behaviors. We designed three distinct configurations (models) of the 3D open field, testing each with single cohorts of sex-matched wild-type (WT) mice. Following initial characterization, two preferred models were selected and tested with cohorts of AS model mice. We found that each model of the 3D open field yielded distinct exploration profiles and transition preferences. In AS mice, we observed reductions in total distance traveled and proportionately fewer large height-difference transitions (leaps), relative to WT controls. AS mice also displayed reduced average velocities while completing leap behaviors. The distinct exploratory patterns associated with each tested model suggest that behavior in the 3D open field can be reliably manipulated through model selection. Additionally, the transition preference phenotype observed in AS mice indicates the 3D open field is capable of capturing subtle motor phenotypes overlooked by standard behavioral measures.

Disclosures: J.J. Shide: None. **C.D. Guoynes:** None. **D. Montgomery:** None. **S. Betts Mendizabal:** None. **M.S. Sidorov:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.02/D21

Topic: A.06. Developmental Disorders

Support: NIH Grant R35GM152057

Title: Investigating the role of CDKL5/LF5 kinase in ciliary length control and disease using Chlamydomonas reinhardtii as a model organism

Authors: *O. OMI[1], Y. HOU[3], G. PAZOUR[4], G. WITMAN[4], K. LECHTRECK[2];
[1]Neurosci., [2]Univ. of Georgia, Athens, GA; [3]UMass Chan Med. Sch., Shrewsbury, MA; [4]UMass Chan Med. Sch., Worcester, MA

Abstract: Mutations in human CDKL5 cause CDKL5 Deficiency Disorder (CDD), characterized by epilepsy and neurodevelopmental delay. Loss of CDKL5 causes cells to build longer than normal cilia, affecting both ciliary signaling and motility. In a murine CDD model, fluid flow above the ciliated ventricular surface is altered, suggesting that cilia malfunction contributes to CDD. To analyze how CDKL5 restricts ciliary growth, we used live-cell imaging, CRISPR gene editing, and biochemistry in the simple unicellular model *Chlamydomonas reinhardtii*. *Chlamydomonas* Long Flagella 5 (LF5) kinase is orthologous to mammalian CDKL5 and *lf5* mutants assemble cilia exceeding wildtype cilia 1.5x in length. Wild-type LF5-GFP was enriched at the ciliary base and only rarely entered the ciliary shaft by intraflagellar transport (IFT), the dedicated protein shuttle of cilia. In contrast, kinase-dead LF5-GFP failed to rescue the long-cilia phenotype and frequently moved by IFT, causing it to redistribute along the ciliary shaft. When expressed in *long flagella 2* (*lf2*), a mutant lacking the conserved ciliary length-regulating kinase LF2/CDK20, LF5-GFP behavior was changed and resembled that of the kinase-dead protein, suggesting that LF2 activates LF5. Indeed, wild-type LF5-GFP obtained from a rescue strain underwent autophosphorylation in vitro whereas autophosphorylation was strongly reduced when LF5-GFP was isolated from *lf2* cilia. Phosphoproteomics identified LF2-dependent phosphorylation at S162, T164, and Y166 in the activation loop of LF5. After substituting these residues with alanine, the mutant LF5-3A-GFP phenocopied kinase-dead LF5-GFP in vivo and in vitro, identifying LF2 as an upstream regulator of LF5. Mammalian and *Chlamydomonas* CDKL5/LF5 possess poorly conserved C-terminal intrinsically disordered regions (IDR). To start exploring the role of the IDR, we expressed LF5-GFP with a partially truncated IDR. LF5-IDR-delt158-GFP failed to rescue the long-cilia phenotype, displayed an altered distribution within cilia, and showed reduced interaction with IFT. We conclude that activity of LF5 kinase critically depends on its IDR. IFT delivers ciliary building blocks fueling ciliary growth, raising the question whether LF5 restricts ciliary length by limiting cargo transport. Live-cell imaging of ARMC2, an
easy-to-image model cargo of IFT, revealed strikingly increased trafficking in *lf5* cilia. We propose that CDKL5/LF5 regulates ciliary length by controlling IFT-dependent cargo delivery and abnormally long cilia resulting from dysregulated ciliary protein transport could contribute to the pathogenesis of CDD.

Disclosures: O. Omi: None. **Y. Hou:** None. **G. Pazour:** None. **G. Witman:** None. **K. Lechtreck:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.03/D22

Topic: A.06. Developmental Disorders

Title: Leveraging Quantitative Phenotyping for Genotype-Phenotype Mapping and Outcome Prediction in Tubulinopathies

Authors: *A. BUTTS;
Neurogenetics, Children's Natl. Hosp., Washington, DC

Abstract: Tubulinopathies are genetically diverse neurodevelopmental disorders with variable neuroanatomical presentations that complicate genotype-phenotype correlation and clinical outcome prediction. Current MRI assessments rely on qualitative descriptions that vary between observers and limit reproducible phenotypic classification. We hypothesized that quantitative neuroanatomical profiling combined with unsupervised hierarchical clustering could provide objective phenotypic groups to improve genotype-phenotype mapping and lay the groundwork for future machine learning-based automation. Structural T1-weighted MRIs (n = 159 from 139 subjects) harboring pathogenic variants in TUBA1A, TUBB, TUBB2A, TUBB2B, and TUBB3 were systematically reviewed by expert readers and converted into quantitative profiles of cortical, basal ganglia, corpus callosum, brainstem, and cerebellar abnormalities. Structural similarity between subjects was quantified using Euclidean distance metrics, and unsupervised hierarchical clustering was subsequently applied to identify phenotypic subgroups. Quantitative phenotyping resolved reproducible classifications consistent with established tubulinopathy spectra. Within the TUBA1A cohort, dysgyria was the most common phenotype (n = 21), followed by severe laminar cortical heterotopia (n = 12) and subtle malformations (n = 5). Clustering identified four principal neuroanatomical groups: subtle cerebellar hypoplasia (Group 1), intermediate dysgyria (Groups 2/3), severe laminar cortical heterotopia (Group 4), and severe lissencephaly (Group 5). Group 4 demonstrated the greatest multisystem involvement, including basal ganglia, corpus callosum, brainstem, and cerebellar abnormalities, with a mean basal ganglia severity score of 2.75. Cross-gene analysis showed that TUBA1A variants span the full phenotypic continuum, whereas TUBB2B variants are most commonly associated with dysgyria and polymicrogyria, TUBB variants are generally associated with milder cerebellar and callosal abnormalities, and TUBB3 variants are primarily associated with congenital fibrosis of the extraocular muscles. These findings demonstrate that quantitative neuroanatomical phenotyping objectively stratifies tubulinopathies and recovers biologically meaningful genotype-phenotype relationships. Ongoing work extends this framework through automated whole-brain segmentation using FastSurfer and deep learning-based feature extraction through BrainIAC to enable scalable, high-throughput phenotyping for biomarker discovery, genotype prediction, and improved clinical outcome prediction.

Disclosures: A. Butts: None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.04/E1

Topic: A.06. Developmental Disorders

Title: Translational Plasma Biomarkers in CDKL5 Deficiency Disorder: new insight from patients, Cdkl5-mutant mice and Human Organoid Models

Authors: *E. MOLTO-RIOS[1], C. J. MALTBY[2], V. PERGHER[2], E. PASCHEN[2], J. PINTO[2], A. KELLERSOHN[2], D. SELLERI[2], M. BIANCHI[2];
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Abstract: Background: CDKL5 Deficiency Disorder (CDD) is a rare X-linked developmental epileptic encephalopathy caused by CDKL5 loss-of-function mutations, resulting in severe cognitive, motor, and behavioural impairments. Robust translational biomarkers linking clinical disease to preclinical models remain limited. CDKL5 regulates microtubule-associated signalling in neuronal development and synaptic plasticity, suggesting cytoskeletal dysfunction biomarkers may offer mechanistically relevant endpoints. We combined clinical biomarker discovery with forward- and back-translational validation across mouse and stem cell-derived models. **Methods:** Plasma from CDD individuals and neurotypical controls was collected via the ELPIS biomarker study. Biomarkers of microtubule dynamics, neurodegeneration, neurotrophic signalling, and inflammation were quantified by Western blotting and ECL ELISA. Parallel analyses were performed in female *Cdkl5* heterozygous and male *Cdkl5* knockout mice using matched plasma and brain panels. iPSC-derived organoids with *CDKL5* mutations and isogenic controls were analysed to determine whether clinical signatures could be recapitulated in a human system. **Results:** Clinical profiling identified elevations in plasma acetylated α-tubulin, neurofilament-light (Nf-L), IL-10, IFN-γ, TNF-α, and IL-1β in CDD versus controls. Acetylated α-tubulin was the most robustly altered biomarker. Similar increases in plasma and brain from *Cdkl5* mutant mice demonstrated cross-species concordance. Organoids with *CDKL5* mutations reproduced key abnormalities from patients and mice, including altered acetylated α-tubulin, Nf-L, IFN-γ, CDKL5, and phosphorylated end-binding protein-2 (pEB2). CDKL5 restoration normalised multiple abnormalities, supporting a direct link between CDKL5 dysfunction and biomarker dysregulation. **Conclusions:** Discoveries were translated from patients into mouse models and back-translated into iPSC organoids. Acetylated α-tubulin emerged as a conserved biomarker across species, tissues, and systems, supporting disrupted microtubule regulation as central to CDD pathophysiology. These findings establish a translational biomarker framework and identify acetylated α-tubulin as a candidate for therapeutic development, target engagement, and future clinical studies.

Disclosures: E. Molto-Rios: None. **C.J. Maltby:** None. **V. Pergher:** None. **E. Paschen:** None. **J. Pinto:** None. **A. Kellersohn:** None. **D. Selleri:** None. **M. Bianchi:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.05/E2

Topic: A.06. Developmental Disorders

Support: K01 MH133970/MH/NIMH NIH HHS/United States
R01 ES034796/ES/NIEHS NIH HHS/United States
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Title: Suppressive Genetic Interactions Between Haploinsufficient Mitochondrial Genes in the 22q11.2 Microdeletion Locus Define Brain and Cardiac Phenotypes

Authors: *E. LIPORACE[1], S. A. ZLATIC[2], M. WYNNE[3], A. CROCKER[5], A. GOKHALE[4], R. PURCELL[6], G. J. BASSELL[7], E. WERNER[1], V. FAUNDEZ[4];
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Abstract: The 22q11.2 microdeletion syndrome reduces dosage of up to 46 protein-coding genes, including eight mitochondrial genes, yet how these genes interact to produce pleiotropic phenotypes remains poorly understood. We tested whether two 22q11.2-encoded mitochondrial genes, the mitochondrial ribosomal protein MRPL40 and the mitochondrial citrate transporter SLC25A1, function as haploinsufficient loci that genetically interact to specify cardiac and brain phenotypes.
In SH-SY5Y, human neuroblastoma cells, MRPL40-null mutations disrupted mitochondrial translation, impaired respiration tested via Seahorse oximetry, elevated mitochondrial dsRNA tested via J2 immunofluorescence, and broadly altered components of the SLC25A1 protein interactome, including mitochondrial ribosome subunits, RNA processing machinery, and lipid metabolism factors. Coessentiality network analysis using FIREWORKS/DepMap identified correlated and anticorrelated fitness interactions linking MRPL40 and SLC25A1 to mitochondrial translation, carbon metabolism, and interferon signaling.
In mice (C57BL/6N, M/F), Mrpl40-null mutations were embryonic lethal, while Mrpl40-/+ heterozygotes were viable. Mrpl40-/+ embryos exhibited ventricular septal defects and noncompaction at E14.5 at frequencies comparable to Slc25a1-/+ animals (~20-31%). Strikingly, transheterozygous Slc25a1-/+;Mrpl40-/+ embryos showed significant suppression of these cardiac defects. In 9-11 week old adult males, Mrpl40-/+ animals displayed hyperactivity at dawn and reduced prepulse inhicbition (PPI) at 82 dB comparable to the Df1/+ 22q11.2 deletion model; both phenotypes were absent in Slc25a1-/+;Mrpl40-/+ transheterozygotes. Bulk RNAseq of microdissected cortex and hippocampus from 9-11 week old adults (n=7-9/genotype) showed that differentially expressed transcripts in single heterozygotes were largely reverted to wild-type

levels in transheterozygous tissue, though a subset of transcripts showed additive changes. These findings demonstrate that MRPL40 and SLC25A1 are haploinsufficient 22q11.2 genes whose combined deficiency unexpectedly suppresses rather than exacerbates cardiac, behavioral, and transcriptomic phenotypes. Our results reveal complex intra-CNV genetic interactions and highlight mitochondrial gene dosage as a key modulator of tissue phenotype penetrance in neurodevelopmental copy number variation syndromes.

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Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.06/E3

Topic: A.06. Developmental Disorders

Support: Institute for Pediatric Rare Diseases, Florida State University

Title: Snord116 expression in the central and peripheral nervous system of mice

Authors: *E. A. HAMMOCK;
Psychology and Program in Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Loss of paternal expression of the non-coding snoRNA *Snord116* causes Prader-Willi Syndrome (PWS). Prior work has demonstrated expression of *Snord116* in the brain, with significant roles in hypothalamic regulation of food intake and metabolism. Here, we report expression of *Snord116* in neurons of the peripheral nervous system (PNS), in addition to expression in the central nervous system (CNS). Using RNAscope in situ hybridization in the whole body of perinatal mice, we show that *Snord116* is expressed exclusively in neurons in the brain, spinal cord, and PNS. *Snord116* co-localizes with the post-mitotic neuronal marker *Rbfox3* (NeuN) in the CNS and PNS. Additionally, in neural crest derived cells of the PNS, *Snord116* also co-localizes in neurons that express *Avil*. At the subcellular level, *Snord116* expression is robust in the cell nucleus, in contrast to the protein-coding transcripts *Rbfox3* and *Avil*, which are distributed in the cytoplasm. Expression of *Snord116* is also detectable in the PNS of adult mice by RT-qPCR. The functional role of *Snord116* in the PNS is currently unknown. Lack of paternal *Snord116* in neurons of the PNS may play a significant role in the earliest emerging PWS phenotypes, including neonatal hypotonia and impairments in sensory-motor reflex circuits needed for infant feeding. Lack of paternal expression of *Snord116* in the PNS may also contribute to elevated pain thresholds and increased aggression and autism-associated sensory phenotypes observed throughout life.

Disclosures: E.A. Hammock: None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.07/E4

Topic: A.06. Developmental Disorders

Support: Mirella and Lino Saputo Foundation
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National Human Genome Research Institute (NHGRI) grants UM1HG008900

Title: Decoding THAP12: Uncovering molecular dysfunction in severe neurodevelopmental epileptic encephalopathy

Authors: *P. K. GUPTA[1], K. OCHENKOWSKA[2], B. RAMPAL[3], A. LÉGARÉ[6], V. TRIASSI[7], S. AUDET[2], A. BRISSON[12], G. BERNAS[8], M. LIAO[9], A. DA SILVA BABINET[9], J. PILLIOD[10], M. GILLASPIE[4], G. VANNOY[13], A. O'DONNELL LURIA[14], N. LECLERC[5], D. WALLEIGH[15], J.-F. SCHMOUTH[7], L. CAPPADOCIA[16], P. DESROSIERS[17], P. DE KONINCK[18], M. TETREAULT[2], E. SAMARUT[11];
[1]Univ. of haifa, Montreal, QC, Canada; [2]Univ. of Montreal, Montreal, QC, Canada; [3]Univ. of Montreal, Longueuil, QC, Canada; [4]Univ. of Montreal, Centennial, CO; [5]Univ. of Montreal, MONTREAL, QC, Canada; [6]Univ. of Laval, Québec, QC, Canada; [7]CRCHUM, Montréal, QC, Canada; [8]CRCHUM, Beloeil, QC, Canada; [9]CRCHUM, Montreal, QC, Canada; [10]CRCHUM, Laval, QC, Canada; [11]NEUROSCIENCES, CRCHUM, Montreal, QC, Canada; [12]Dept. of Chem., Univ. of Quebec in Montreal, Montreal, QC, Canada; [13]Broad institute, Aliso Viejo, CA; [14]Broad institute, Boston, MA; [15]Children's Hosp. Colorado, Aurora, CO; [16]Univ. du Québec à Montréal, Montréal, QC, Canada; [17]Physics, Univ. Laval, Québec, QC, Canada; [18]Cell. Neurobio., Univ. Laval, Quebec, QC, Canada

Abstract: Lennox-Gastaut syndrome (LGS) is a severe developmental epileptic encephalopathy (DEE) caused by rare genetic variants disrupting brain development and excitability, yet its cause remains unknown in approximately 30% of cases. We used human genomic sequencing, in vivo animal models, and transcriptomic profiling to identify *THAP12* as a novel causal gene for autosomal recessive DEE. Whole-genome sequencing in two affected siblings presenting with LGS revealed compound heterozygous variants in *THAP12*, associated with reduced protein abundance consistent with a loss-of-function (LOF) mechanism. Patient-specific allele mouse models confirmed the dosage-sensitive and essential role of *Thap12* during early development, as both homozygous and compound heterozygous animals exhibited embryonic lethality. To define the developmental window of *Thap12*, conditional knockout (cKO) mice using a Nestin-Cre driver were generated, enabling phenotypic analyses across corticogenesis (E12.5-E18.5). RNAscope analyses of wild-type E12.5 embryos reveal that *Thap12* is highly enriched in Sox2-positive ventricular zone progenitors and largely absent from mature cortical layers, identifying neural progenitors as a primary site of action. In parallel, zebrafish LOF models recapitulated key human phenotypes, including microcephaly, brain hypoplasia, abnormal neuronal activity, and increased seizure sensitivity. Transcriptomic profiling of larval zebrafish brains revealed

dysregulation of cell cycle and apoptotic pathways, consistent with increased cell death and reduced proliferation in mutant embryos. Overexpression of wild-type human *THAP12* mRNA rescued these phenotypes, whereas patient-derived variant alleles failed to do so. These findings demonstrate that *THAP12* is essential for neural progenitor function and cortical development, provide the first mechanistic framework linking *THAP12* dysfunction to epilepsy, and open new avenues for diagnosis in unsolved DEE cases.

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Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

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Program #/Poster #: PSTR041.08/E5

Topic: A.06. Developmental Disorders

Support: NIH UG3TR004713
NIH UG3/UH3NS115597
FAST

Title: Brain-Wide Non-Viral Genome Editing for Angelman Syndrome

Authors: *X. LU, Y.-H. JIANG;
Genet., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Gene editing offers the potential to treat and even cure neurogenetic disorders, but brain-wide delivery of genome-editing therapeutics remains a major challenge. To overcome limitations of AAV- and LNP-based CNS delivery, we developed Stimuli-Responsive Traceless Engineering Platform (STEP), a non-viral, non-nanoparticle, chemical modification-based platform for CRISPR/Cas9 ribonucleoprotein (RNP) delivery. The small size of STEP-RNP (12-14 nm) enables broad brain distribution, while cholesterol-based modifications promote neuronal delivery and transient intracellular Cas9 exposure minimizes off-target risk. We applied STEP-RNP to Angelman syndrome (AS), a severe neurogenetic imprinting disorder caused by deficient maternal *UBE3A* expression in neurons. Paternal *UBE3A* is silenced by the *UBE3A* antisense transcript (*UBE3A-ATS*). Although ASOs targeting *UBE3A-ATS* have shown clinical promise, their molecular effects are transient and moderate. STEP-RNP was therefore designed to disrupt *UBE3A-ATS* and reactivate paternal *UBE3A*. In AS mice, a single intrathecal injection (IT) at P1, P21, or P42 significant reduced *Ube3a-ATS* and restored *Ube3a* expression to as much as 81% of normal across the cortex, hippocampus, and cerebellum. Treatment produced durable functional

rescue, improving locomotion, anxiety-like behavior, learning and memory, chemically induced myoclonic and tonic seizure latency, and EEG phenotypes. In AS patient iPSC-derived cortical organoids, a single STEP-RNP treatment efficiently inactivated *UBE3A-ATS* and robustly reactivated paternal *UBE3A.* We next evaluated STEP-RNP delivery in non-human primates (NHPs). Radiolabeled Cas9 PET imaging demonstrated brain-wide distribution after IT, intracisterna magna, and intracerebroventricular (ICV) administration, with the broadest distribution achieved by ICV delivery. STEP-RNP carrying a human *UBE3A-ATS*-targeting single guide (sg)RNA efficiently inactivated *UBE3A-ATS* and reactivated *UBE3A* across the NHP brain. SNP-based allele-specific analysis showed 75-95% paternal allele expression as early as 4 days after administration, with durable persistence through the final observation timepoint months after. Paternal gene expression exceeded levels reported for ASO approaches in NHPs. STEP-RNP was well tolerated in mice, and extensive analyses of treated iPSC neurons revealed no significant off-target events. Dose-ranging toxicology studies in NHPs are ongoing. Together, these findings support STEP-RNP as a promising gene-editing therapeutic strategy for AS and a broadly applicable CNS delivery platform for neurogenetic disorders.

Disclosures: X. Lu: F. Consulting Fees (e.g., advisory boards); Couragene, Inc, CourageAS, Inc. **Y. Jiang:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.09/E6

Topic: A.06. Developmental Disorders

Support: NIH Grant 1R21NS142525-01

Title: Unraveling the Mechanisms of RHOBTB2-associated Developmental and Epileptic Encephalopathy

Authors: *A. OLSZEWSKI, S. PRUETT-MILLER, H. MEFFORD;
St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Heterozygous missense variants in the gene *RHOBTB2* cause a developmental and epileptic encephalopathy (RHOBTB2-DEE), characterized by epilepsy, intellectual disability, and movement disorders. Three recurrent variants, R483H, R511W, and R511Q, account for ~70% of RHOBTB2-DEE cases. Individuals with heterozygous *RHOBTB2* loss-of-function variants are healthy, whereas those with biallelic loss-of-function variants have neurological presentations that are generally milder than RHOBTB2-DEE. Based on the genotype-phenotype relationship, we hypothesize that DEE variants in *RHOBTB2* have a toxic gain-of-function or a dominant-negative mechanism. RHOBTB2 is a substrate adaptor protein for CUL3, an E3 ubiquitin ligase, but little is known about how RHOBTB2-DEE variants affect its function. Our investigation aims to determine the molecular and cellular consequences of RHOBTB2-DEE

variants and to evaluate the therapeutic potential of antisense oligonucleotides (ASOs) for RHOBTB2-DEE. RHOBTB2-DEE variant proteins have increased abundance due to impaired degradation. We showed that R511W, which had not been previously tested, also exhibits this increased abundance. We examined the effects of RHOBTB2-DEE variants on cellular and molecular processes affected by *RHOBTB2* loss using a set of isogenic SF126 glioblastoma cell lines with engineered *RHOBTB2* variants (WT/WT, WT/-, WT/R483H, WT/R511Q, WT/R511W). Knockdown of *RHOBTB2* impacts intracellular transport. Using an eGFP-tagged VSVG system, we determined that the RHOBTB2-DEE variants had altered ER-to-Golgi-to-membrane transport. In contrast to what occurs in *RHOBTB2* knock-out cells, RHOBTB2-DEE SF126 lines showed increased VSVG localization at the Golgi. We hypothesized that this is due to increased speed of ER-to-Golgi transport or impaired Golgi exiting. To identify biological processes affected by RHOBTB2-DEE, we performed RNA-seq. Comparison between the DEE (WT/R483H, WT/R511Q, WT/R511W) lines and the non-DEE (WT/WT, WT/-) lines revealed downregulation of genes involved in the regulation of neuron projection development, extracellular matrix organization, integrin binding, and axonogenesis. We designed gapmer ASOs targeting RHOBTB2-DEE variants to achieve allele-specific RNA degradation. Testing in SF126 models showed successful knockdown of *RHOBTB2* by ASOs, but this knockdown was surprisingly not allele-specific. Our next steps include characterizing patient iPSC-derived 2D neurons and mass spectrometry identification of binding partners of RHOBTB2, with and without DEE-variants. *In vitro* RHOBTB2-DEE models enable insight into disorder pathomechanisms.

Disclosures: A. Olszewski: A. Employment/Salary (full or part-time):; St. Jude Children's Research Hospital. **S. Pruett-Miller:** A. Employment/Salary (full or part-time):; St. Jude Children's Research Hospital. **H. Mefford:** A. Employment/Salary (full or part-time):; St. Jude Children's Research Hospital.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.10/E7

Topic: A.06. Developmental Disorders

Support: DeNardo Education & Research Foundation

Title: CTBP1 Dysregulates Master Metabolic Regulators in Isogenic Human Neurons

Authors: *S. GODHANI[1], R. CARTER[1], Y. SA[2], U. EZEKIEL[1];
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Abstract: C-terminal binding proteins (CtBP1 and CtBP2) are highly conserved vertebrate transcriptional corepressors with overlapping, yet distinct roles in development. They mediate these roles through multiple protein-protein interactions that recognize specific consensus

sequences on partner proteins, including the Pro-Leu-Asp-Leu-Ser (PLDLS) motif, the Arg-Arg-Thr (RRT) motif, and PDZ-binding motifs. In the presence of NADH, CtBPs form homo- or heterodimers that use conserved PLDLS- and RRT-binding motifs to assemble corepressor complexes. This recruitment is largely facilitated by a high-affinity, hydrophobic PLDLS-binding cleft. Once assembled, the CtBP complex directs coordinated epigenetic gene silencing through histone modifications. A recently identified de novo missense mutation in CTBP1 is clinically associated with a neurodevelopmental syndrome characterized by Hypotonia, Ataxia, Developmental Delay, and Tooth-Enamel Defects (HADDTS). The majority of these patients harbor a heterozygous missense mutation in the CTBP1 (c.991 C → T, p.R331W in NM_001012614.1; c.1024 C → T, p.R342W in NM_001328.2) gene, which is often associated with early onset profound cerebellar atrophy. This arginine-to-tryptophan substitution at the C-terminal edge of the PLDLS pocket alters the PLDLS-binding cleft, thereby impairing chromatin modification and downstream gene expression. To investigate this phenotype, we generated neurons from neural stem cells (NSCs) derived from induced-pluripotent stem cells (iPSCs). Patient-derived iPSCs and unrelated age-matched controls can introduce confounding variables such as genetic background variation, disease penetrance, and environmental influences. These factors may mask or distort the true functional outcomes of the mutation. Under normal physiological conditions, rising intracellular NADH indicates glycolytic abundance, promoting active CtBP1 homodimerization and subsequent transcriptional repression of metabolic regulators. Our preliminary data indicate that both 4-EBP1 and p70 S6 Kinase phosphorylation are suppressed, signifying that the mechanistic target of rapamycin complex 1 (mTORC1) is affected, and AMP-activated protein kinase (AMPK) phosphorylation is increased. For the first time, our results show that CTBP1 mutation dysregulates both AMPK and mTORC1 pathways. This suggests that structural distortion of the interaction interface in the p.R342W mutant hinders key genes involved in regulating major pathways, triggering an unexpected homeostatic stress cascade. Future studies aim to understand how the CTBP1 mutation destabilizes metabolic pathways.

Disclosures: S. Godhani: None. **R. Carter:** None. **Y. Sa:** None. **U. Ezekiel:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.11/E8

Topic: A.06. Developmental Disorders

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

Title: Temporal evolution of network dynamics surrounding tics in Tourette syndrome

Authors: *G. LOWOR[1], J. GOMEZ[2], M. HOOK[3], T. A. HARLAND[4], C. R. BUTSON[5], K. FOOTE[3], M. OKUN[3], A. GUNDUZ[2];
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[4]Lab. of Quantitative Neuromorphology, The Colorado Col., Colorado Springs, CO; [5]Norman Fixel Inst. for Neurolog. Dis., Fixel Inst., Gainesville, FL

Abstract: Tourette syndrome (TS) is a neurological disorder marked by involuntary, repetitive movements and vocal sounds known as tics. For patients with moderate to severe motor and vocal tics, especially those with other comorbidities who become refractory to typical medication and behavioral therapies, deep brain stimulation (DBS) has become a possible treatment option. Therefore, understanding how deep brain circuits interact during tic generation will help improve our knowledge of TS and DBS therapy. This study aims to examine how two key DBS structures: the centromedian thalamus (CM) and anterior globus pallidus internus (aGPi), interact before and after tic occurrence in Tourette syndrome. Seven patients with TS (average age 22.3±4.9 years) participated in the study, each with bilateral 4-contact-level electrodes implanted in the CM and aGPi, for a total of 16 leads. These were connected ipsilaterally to two neurostimulators with adaptive DBS (aDBS) capabilities (Medtronic Percept PC, Minneapolis, MN) under an FDA IDE. Preoperative MRI and postoperative CT scans localized the electrode placements. Participants attended monthly clinic visits over 9 months, during which neural signals were recorded under pre-tic, post-tic, surrogate, and non-tic conditions, with no stimulation during the first 3 months. We found that coherence between these regions—rather than local activity alone—best distinguishes tic-related states ($p<0.05$ in both hemispheres). Low-frequency (<10 Hz) coherence dominated and showed clear hemispheric asymmetry, with the left hemisphere capturing transitions around tic onset and the right differentiating tic from rest. Beta (13-30 Hz) activity reflected general engagement, whereas low-gamma (30-50 Hz) activity was most prominent after tics, suggesting recovery processes. Notably, network activity normalized quickly after the tic was executed ($p=1$). These findings highlight frequency-specific network dynamics as key mechanisms underlying tic generation and provide a foundation for developing targeted, adaptive DBS strategies in TS.

Disclosures: G. Lowor: None. **J. Gomez:** None. **M. Hook:** None. **T.A. Harland:** None. **C.R. Butson:** None. **K. Foote:** None. **M. Okun:** None. **A. Gunduz:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.12/F1

Topic: A.06. Developmental Disorders

Support: DeNardo Education and Research Foundation

Title: Early Developmental Stages of Cerebellar Granule Cell Differentiation Are Disrupted by CTBP1 Mutation

Authors: *N. TRINH[1], S. GODHANI[1], U. EZEKIEL[1,2];
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Abstract: C-terminal Binding Protein 1 (CtBP1) is a transcriptional coregulator that plays essential roles in neurodevelopment by regulating gene expression programs involved in neuronal differentiation and maturation. CtBP1 functions primarily as a transcriptional corepressor, recruiting chromatin-modifying factors to promoter-bound repressors. A heterozygous pathogenic missense mutation in *CTBP1* was recently identified as causing Hypotonia, Ataxia, Developmental Delay, and Tooth Enamel Defects Syndrome (HADDTS), a rare neurodevelopmental disorder frequently associated with early-onset cerebellar atrophy. Although cerebellar abnormalities are a prominent clinical feature of HADDTS, the developmental mechanisms linking *CTBP1* dysfunction to cerebellar pathology remain poorly understood. Previous studies in mice and data from the Allen Brain Cell Atlas demonstrate that CtBP1 is highly expressed in the upper rhombic lip (URL), the developmental region that gives rise to cerebellar granule cells (CGCs). These cells represent the most abundant neuronal population and are critical for normal cerebellar development and function. Therefore, we hypothesized that *CTBP1* mutations impair CGC development. To investigate the role of CtBP1 during cerebellar development, we differentiated isogenic wild-type and *CTBP1*-mutant induced pluripotent stem cell (iPSC) lines into early CGCs and examined developmental progression at multiple stages of differentiation using immunocytochemical analyses of Atonal Homolog 1(ATOH1), Zinc Finger of the Cerebellum 2 (ZIC2), and Ki-67, together with βIII-tubulin to measure neurite length. *CTBP1*-mutant cells displayed altered temporal expression patterns of key CGC developmental markers. Relative to wild-type cells, mutants exhibited reduced expression of a transcription factor, ATOH1, which specifies early stages of differentiation, suggesting a delay in the developmental progression required for CGC specification. The expression patterns of the transcription factor ZIC2 and the proliferation marker Ki-67 were also altered, consistent with impaired granule cell lineage progression. In addition, *CTBP1*-mutant cells developed significantly longer neurites, indicating abnormal neuronal maturation. Transcriptome analysis further revealed downregulation of genes associated with early rhombic lip generation and cerebellar granule cell development, supporting the cellular findings. Together, these results demonstrate that the *CTBP1* mutation disrupts the developmental program of early CGC differentiation.

Disclosures: N. Trinh: None. **S. Godhani:** None. **U. Ezekiel:** None.

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.13/F2

Topic: A.06. Developmental Disorders

Support: FPWR Grant 1199546-1-104577

Title: Integrative Fine-Mapping and Chromatin Architecture Analyses Reveal Regulatory Organization of the Prader-Willi Syndrome (PWS) Locus

Authors: *Z. AGHA[1], S. WANG[2], J. B. WILLIAMS[3];
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Abstract: Integrative Fine-Mapping and Chromatin Architecture Analyses Reveal Regulatory Organization of the Prader-Willi Syndrome (PWS) LocusPrader-Willi syndrome (PWS) results from disruption of the imprinted 15q11.2-q13 region and is characterized by complex neurodevelopmental and metabolic phenotypes. Although multiple genes within this interval have been implicated in disease pathogenesis, the higher-order chromatin organization of the PWS locus and its relationship to regulatory variation remain poorly understood. We integrated neuroimaging genetics, statistical fine-mapping, and Hi-C chromatin interaction analyses to define the three-dimensional regulatory architecture of 15q11-q13. GWAS of structural MRI phenotypes in approximately 10,000 children from the ABCD cohort identified significant associations within the PWS region. Transcriptome-wide association and SuSiE-RSS fine-mapping prioritized multiple regulatory intervals spanning imprinted, noncoding, and synaptic loci.Hi-C analyses revealed that the PWS interval resides within a conserved chromatin domain spanning approximately chr15:23.7-29.0 Mb, with reproducible TAD boundaries across pancreatic alpha, beta, and acinar cells. Within this shared scaffold, interaction strength varied by cell type, with beta cells showing the strongest intra-domain contacts. In the brain, 18,834 loops involved the PWS region, including 16,869 NeuN-positive-specific loops, demonstrating marked neuronal enrichment. Loop anchors involved key PWS candidate genes, including MAGEL2, NDN, and NPAP1, and partially overlapped fine-mapped regulatory intervals. In addition, neuron-specific trans contacts linked the BP2-BP3 interval to olfactory receptor clusters across multiple chromosomes. These findings demonstrate that the PWS locus is embedded within a conserved three-dimensional chromatin domain characterized by extensive neuron-enriched looping and tissue-specific interaction dynamics. Together, the results support a model in which disruption of chromatin architecture contributes to the broad neurodevelopmental and metabolic manifestations of PWS.

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

Poster

PSTR041: Angelman and Other Developmental Disorders

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR041.14/F3

Topic: A.06. Developmental Disorders

Support: NIH grants R01NS97846, R01NS097846-02S1, R01NS092876 and NIAAA of NIH grant R01AA031319 to MS

Title: Regulation of MicroRNA-Targeted Gene Expression: Neurotoxicity Biomarkers in Fetal Brain Exosomes in Blind Studies for Fetal Alcohol Spectrum Disorders

Authors: *L. DRAK[1], T. SA NGUANPHO[1], M. HAMPE[1], U. BHARAI[1], J. HAMZE[4], J. HU[1], S. HASSAN[1], E. OLIVER[1], R. MOSSABEB[6], M. F. MORRISON[8], L. HART[7], N. DARBINIAN[2], M. E. SELZER[3], H. ZHAO[5];
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Abstract: Neuronal growth plays a critical role in synaptic development, metabolic support, and neurotrophic signaling during fetal brain maturation. Prenatal alcohol exposure disrupts these interactions, yet early, non-invasive biomarkers of such alterations remain limited. This study investigates microRNAs involved in neurotoxicity events caused by prenatal alcohol exposure within fetal brain-derived exosomes (FB-Es) isolated from maternal blood as potential early predictors of fetal alcohol spectrum disorders (FASD).

Disclosures: L. Drak: None. **T. Sa Nguanpho:** None. **M. Hampe:** None. **U. Bharai:** None. **J. Hamze:** None. **J. Hu:** None. **S. Hassan:** None. **E. Oliver:** None. **R. mossabeb:** None. **M.F. Morrison:** None. **L. Hart:** None. **N. Darbinian:** None. **M.E. Selzer:** None. **H. Zhao:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.01/F4

Topic: A.07. Development of Neural Systems

Support: 5R01NS126981

Title: Blood-Brain Barrier maturation generates a critical period for fetal serotonergic neurodevelopment

Authors: *C. AKIZ[1,2], A. BONNIN[1,2];
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Abstract: During fetal development, the emerging blood-brain barrier (BBB) may regulate delivery of trophic factors from the blood to the brain. We propose that placentally-derived serotonin is such a factor, regulating processes such as axon growth and guidance in the fetal forebrain. Maternal Immune Activation (MIA) in mice at embryonic day (E)12 increases placental serotonin release into the blood circulation and fetal forebrain serotonin levels, selectively blunting rostral serotonergic axon outgrowth at E14. Specific effects of blood serotonin on fetal forebrain development likely depend on regional BBB permeability and maturation. MIA has been associated with altered serotonin concentration in the brain of the

adult offspring and increased risk of schizophrenia in humans. Thus, the prenatal timing of MIA and BBB maturation may affect canonical neuronal circuit formation. We aim to understand developmental changes resulting from MIA on the serotonin system, and to identify molecular drivers of BBB maturation by using ex vivo and in vivo permeability assays to map fetal BBB maturation across mid to late gestation.Serotonin (~0.2 KDa) was perfused ex vivo via the umbilical vein of E14 mouse embryos for 10 minutes, followed by a washout. Serotonin concentration in the forebrain and hindbrain was measured by HPLC. To further characterize regional BBB maturation, embryos were perfused ex vivo with fluorescent tracers (10 and 40 KDa) and parenchymal distribution of fluorescence analyzed by microscopy. To investigate potential molecular drivers of BBB maturation, we mined publicly available bulk RNA-seq data to compile differentially expressed forebrain and hindbrain genes from E13 to E16.Ex vivo perfusions of serotonin show a 16.3+/-7.1-fold increase in the forebrain and 5.2+/-2.5-fold increase in the hindbrain compared to vehicle (n=3). Fluorescent tracer perfusions suggest higher permeability in the cerebral cortex compared to the hindbrain. Furthermore, permeability to these tracers is limited to specific brain regions that change over time. Bulk RNA-seq analysis revealed candidate genes with differential expression in forebrain vs hindbrain over time, potentially associated with a caudal to rostral gradient of BBB maturation.We uncover a functional maturation of fetal BBB using fluorescent tracers in high spatial resolution. Our serotonin perfusions support the idea that the immature BBB in the forebrain is permeable to serotonin. Our investigation of functional and pathophysiological interactions between BBB maturation and serotonergic system development will identify early critical periods for neural circuit the development in the fetal brain

Disclosures: C. Akiz: None. **A. Bonnin:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.02/F5

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

Title: Alterations in blood brain barrier function and microglia in a mouse model of Alzheimer's disease

Authors: *L. HOU[1], J. CHENG[1], T. TSUJI[1], I. TAKEDA[1], A. J. MOORHOUSE[2], H. WAKE[1,3,4,5];
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid-beta deposition and tau pathology. Recent Gd-MRI studies suggest that blood-brain barrier (BBB) alterations occur at early stages of AD. However, the temporal sequence of BBB disruption and the cellular mechanisms underlying these changes remain unclear.
Here, we investigated the temporal relationship between microglial BBB association, astrocyte-derived signaling, and BBB dysfunction in APP knock-in mice. In vivo two-photon microscopy revealed an increase in BBB permeability at 13-14 weeks of age, accompanied by tight junction loss confirmed by electron microscopy. Notably, microglia accumulated around vessels at approximately 11 weeks, before detectable BBB leakage.
Time-series RNA sequencing of microglia and astrocytes revealed progressive changes in genes associated with migration, adhesion, inflammation, and vessel interaction. In microglia, Mmp14 was prominently upregulated during the period of BBB dysfunction, identifying it as a candidate effector of BBB disruption. Consistently, treatment with an MMP inhibitor improved BBB disruption, supporting a functional contribution of MMP activity to BBB dysfunction.
Meanwhile, astrocyte RNA-seq showed dynamic changes in genes associated with vessel interaction and extracellular signaling, highlighting candidate astrocyte-derived cues that may facilitate microglial recruitment and adhesion prior to BBB dysfunction. AAV-mediated knockdown of astrocytic Gas6 reduced BBB leakage, suggesting that astrocyte-derived Gas6 signaling contributes to BBB dysfunction in APP knock-in mice.Single-cell RNA sequencing identified an APP-enriched microglial cluster with upregulated Mmp14 and DAM-associated genes, showing vascular remodeling signatures and preferential Axl expression, linking this microglial state to BBB disruption and potential Gas6-Axl response. We are currently investigating whether Gas6-Axl signaling also affects downstream Aβ accumulation.

Disclosures: L. hou: None. **J. cheng:** None. **T. Tsuji:** None. **I. Takeda:** None. **A.J. Moorhouse:** None. **H. Wake:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.03/F6

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

Support: P01AG078116

Title: Astrocyte GLT-1 at the Interface Between Neuronal Activity, Neurovascular Unit Integrity, and Functional Hyperemia in Alzheimer's Disease

Authors: *B. E. WEISS[1], J. GOLLIHUE[2], E. B. RUCKER, III[3], S. D. KRANER[1], J. C. GANT[4], C. B. ROGERS[5], P. SOMPOL[6], C. M. NORRIS[5];
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Abstract: Astrocytes protect neurons from excitotoxicity by clearing synaptic glutamate through GLT-1/EAAT2 transporters, while regulating metabolic homeostasis and supporting neurovascular unit function. GLT-1/EAAT2 expression declines in mild cognitive impairment and Alzheimer's disease (AD), coinciding with early cortical hypoperfusion and neurovascular dysfunction. However, how astrocyte glutamate transport shapes astrocyte physiology, endfoot integrity, and vascular function remains unclear. Here, we tested whether altered astrocyte GLT-1 expression contributes to impaired activity-dependent neurovascular signaling.
2-3-month-old 5xFAD mice and littermate controls received retro-orbital PHP.eB-GFA2-GLT1 or PHP.eB-GFA2-Luciferase. Five months later, cranial windows were implanted over barrel cortex and mice received cortical AAV2/5-GFA104-jGCaMP8f to label astrocyte calcium activity. Four weeks later, awake two-photon imaging and laser speckle contrast imaging were performed during vibrissae air-puff stimulation to measure astrocyte calcium signaling, vessel dynamics, and cerebral blood flow responses. Activity was segmented using the STONE-LAVA framework. In a complementary loss-of-function experiment, GLT-1 floxed mice received AAV2/5-GFA104-Cre recombinase in one cortical hemisphere and AAV2/5-GFA2-Luciferase in the contralateral hemisphere, followed by longitudinal imaging over three months. Tissue was labeled for markers of blood-brain barrier integrity, astrocyte reactivity, endfoot organization, and Aβ pathology.
5xFAD mice exhibited significant impairments in neurovascular coupling, astrocyte calcium signaling dynamics, and astrocyte network synchrony. Region-specific GLT-1 deficiency produced hyperactive astrocyte calcium signaling and altered hyperemic responses, suggesting that astrocyte glutamate transport regulates astrocyte excitability and vascular output.
Histological analyses assessed neurovascular unit-associated markers including DP71 and aquaporin-4, as well as GFAP and Aβ pathology, to determine whether functional changes were accompanied by altered astrocyte reactivity, endfoot organization, and blood-brain barrier-associated structure.
These findings support a model in which astrocyte GLT-1/EAAT2 links synaptic glutamate handling to astrocyte calcium dynamics, neurovascular unit integrity, and functional hyperemia. Loss of astrocyte glutamate transport may contribute to astrocyte-vascular dysfunction through altered activation patterns and structural disruption at the neurovascular interface.

Disclosures: B.E. Weiss: None. **J. Gollihue:** None. **E.B. Rucker:** None. **S.D. Kraner:** None. **J.C. Gant:** None. **C.B. Rogers:** None. **P. Sompol:** None. **C.M. Norris:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.04/F7

Topic: D.04. Brain Injury and Trauma

Support: Nashman Institute Grant BD0001

Title: Immunomodulation affects astrocyte heterogeneity and accelerates development in iPSC-derived brain organoids

Authors: *Z. NASHMAN[1], V. C. OGBOLU[2], L. QIANG[3];
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Abstract: Background: Brain Organoids generated from induced pluripotent stem cells are currently of great interest for the purposes of brain repair due to it's three dimensional architecture and it's ability to be transplanted into injured brain cavities. However, astrocytes, the major glial cell found in native brain are not found in sufficient quantities and nor do they morphologically match native brain astrocytes. Due to the abundant interaction astrocytes have with neurons in the native brain, immunomodulation may have the potential to drive astrocyte maturation and morphology present in brain organoids. The immunoproteasome may have a role in driving unregulated pro-inflammatory phenotype which may affect its maturation. LMP7 is a major part of the immunoproteasome and it's inhibition can attenuate this effect.
Hypothesis: Treatment of human organoids with an LMP7 inhibitor will accelerate astrocyte maturation and morphology identical to human brain.
Methods: Human brain organoids were generated from pluripotent stem cells and maintained under standard culture conditions for 5 months to allow for cellular maturation. At the conclusion of the maturation period, organoids were exposed to an LMP-7 inhibitor for 48 hours, while control organoids received vehicle treatment. Following treatment, organoids were fixed, cryoprotected. Frozen sections were prepared at standardized thicknesses of 20 microns and processed for immunofluorescence staining using antibodies against glial fibrillary acidic protein (GFAP). Stained sections were imaged using confocal microscopy, and qualitative and/or quantitative analyses of GFAP expression were performed to evaluate the effects of LMP-7 inhibition on astrocyte-related cellular responses within the organoid model. Total number of astrocytes were unchanged between the two groups.
Results: There was an increase in GFAP signal intensity in the treatment group by 17.5%. The treatment group did not show more damage compared to the untreated group. Scholl analysis showed peak number of intersections to be 21 microns in the treatment group versus 33 microns in the control group. There was a 35% increase in astrocyte process thickness. Total number of astrocytes were the same in both groups. Conclusion: Immunomodulation in brain organoids can make a replica of human brain tissue by accelerating the maturation of astrocytes as ascertained through the increased GFAP expression. Interestingly, scholl analysis shows decreased mean number of intersections, which may suggest developing phenotype of a different cortical layer compared to control organoids.

Disclosures: Z. Nashman: None. **V.C. Ogbolu:** None. **L. Qiang:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.05/F8

Topic: A.07. Development of Neural Systems

Support: R01 MH128745

Title: Coordinated astrocyte-neuron transition across a delayed maturation window in the amygdala

Authors: *K. SHIMODA, S. R. JETT, J. ISENBERG, J. BAROUDI, S. F. SORRELLS; Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The amygdala, a region important for social and emotional processing, contains a population of embryonically born excitatory neurons that retain immature morphological and molecular features for weeks in mice and decades in humans. It is unknown whether the protracted maturation of this doublecortin (Dcx)-expressing excitatory population is sustained by the microenvironment. We hypothesize that local astrocytes supply age-specific support that maintains the immaturity of the region. Using immunohistochemistry across an age series in mice (P7-P35) and in human postmortem tissue from infancy to adulthood, we characterize the postnatal trajectory of amygdala astrocytes in the region of late-maturing neurons. We find that the astrocyte structural glial fibrillary acidic protein (GFAP) is highly expressed at P14 and declines in parallel with Dcx expression, along with no change in the number of S100β+ astrocytes. Single-nucleus RNA sequencing across postnatal development (P7-60), reveals age-dependent changes in astrocyte gene expression during this late window of amygdala neuron maturation. Interestingly, early life stress (ELS) seems to not impact GFAP downregulation with age, but promotes increased Dcx retention. In humans, there appears to be a decrease in GFAP+ process thickness from birth to adulthood, but in adults they are consistently thin (21 years to 77 years). Together, these data suggest astrocyte developmental state may be instructive for the completion of neuronal maturation in this region and that these processes may be transiently altered with ELS. Understanding the molecular identity and functional specialization of PL astrocytes will reveal new mechanisms by which the local glial microenvironment regulates the timing of postmitotic neuronal maturation, with implications for how early life experience shapes amygdala circuit development.

Disclosures: K. Shimoda: None. **S.R. Jett:** None. **J. Isenberg:** None. **J. Baroudi:** None. **S.F. Sorrells:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.06/G1

Topic: A.04. Transplantation and Regeneration

Support: McKnight Foundation

Title: Combinatorial deletion of nuclear factor I and RBPJ unlocks injury-independent astrocyte-to-neuron reprogramming in adult cortex

Authors: *Y. CHEN[1], T. HOANG[2];
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Abstract: Irreversible neuronal loss is a common pathological consequence of central nervous system injury and neurodegenerative disease, yet the adult mammalian brain has limited capacity for neuronal replacement. In situ astrocyte-to-neuron reprogramming is a potential regenerative strategy because astrocytes are abundant, regionally distributed, injury responsive, and amenable to viral targeting. However, current approaches remain limited by inefficient conversion, uncertain lineage fidelity, incomplete maturation, poor subtype control, and regional differences in competence. Strategies that improve astrocyte competence, neuronal conversion, and survival are therefore needed.To test whether nuclear factor I (NFI) transcription factors and RBPJ-dependent Notch signaling jointly restrict astrocyte neurogenic competence, we conditionally deleted Nfia, Nfib, Nfix, and Rbpj in adult cortical astrocytes. Combined deletion of NFI factors and Rbpj induced robust reprogramming in the intact cortex, with astrocytes undergoing dedifferentiation, entering proliferation-associated states, and generating immature neurons. Single-cell analysis revealed a trajectory from astrocytes through neural stem cell-like intermediates to immature neuronal states with prominent GABAergic interneuron-like features. In contrast, deletion of either pathway alone produced a more limited neurogenic response, supporting a cooperative role for NFI factors and RBPJ-dependent Notch signaling in restricting neuronal conversion from adult cortical astrocytes.Despite efficient induction of neuronal fate, many newly generated cells failed to persist as immature neurons. Immunohistochemistry showed that microglia in the reprogrammed cortex exhibited reduced process arborization and increased CD68 expression, were frequently located near newly generated immature neurons, and in some cases contained intracellular DCX-positive puncta. Microglia depletion further increased DCX-positive neuroblasts and HuC/D-positive neurons at later time points, suggesting that microglia-associated phagocytic activity contributes to the loss of newly generated immature neurons.These data show that combined NFI and Rbpj deletion promotes injury-independent neuronal production from adult cortical astrocytes and implicate microglia-associated phagocytic activity as a barrier to the survival of newly generated immature neurons. Improving in vivo reprogramming may require both transcriptional enhancement of astrocyte competence and protection of newly generated neurons as they mature, acquire subtype identity, and integrate into host circuits.

Disclosures: Y. Chen: None. **T. Hoang:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.07/G2

Topic: I.04. Executive Functions

Support: NRF-2017R1A5A1014708
No. 2022M3E5E9018226
KBRI / 22-BR-02-02
NRF - RS-2024-00460958

Title: Psilocybin modulates nucleus accumbens activity via astrocytic transcriptional regulation

Authors: *D.-S. KANG[1], J. KOO[2], S. CHANG[5], S. KANG[1], T.-Y. CHOI[3], S. JEONG[4], Y. JEONG[6], C. LEE[7], K. KIM[8];
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Abstract: Psilocybin alters neural activity and inhibitory balance within mesolimbic circuits, yet the cellular mechanisms underlying these effects remain incompletely defined. Here, we combined *in vivo* electrophysiology, neurochemical analysis, and molecular profiling to investigate how psilocybin regulates inhibitory tone in the nucleus accumbens. Psilocybin increased neuronal firing while consistently reducing extracellular GABA levels, indicating a shift toward circuit disinhibition.To identify the underlying mechanism, we performed transcriptomic and chromatin analyses, which revealed induction of the Ca^{2+}-dependent transcription factor NFATc4 and increased histone acetylation. Cell-type-specific analyses demonstrated that these changes occurred selectively in astrocytes, where psilocybin elevated NFATc4 expression, enhanced H3K27ac, and increased transcriptional regulation of GABA metabolic pathways, including the *Aldh5a1* locus. This was associated with reduced intracellular GABA levels in astrocytes, whereas neuronal GABA remained unchanged.Mechanistically, calcium signaling triggered by the active metabolite of psilocybin was dependent on 5-HT2A receptor activation, linking receptor engagement to NFATc4-mediated transcriptional regulation. Together, these findings identify an astrocyte-specific NFATc4-dependent epigenetic mechanism that is associated with the regulation of GABA metabolism and contributes to disinhibition of mesolimbic circuitry, redefining the cellular and circuit basis of psilocybin action in mesolimbic systems.

Disclosures: D. Kang: None. **J. Koo:** None. **S. Chang:** None. **S. Kang:** None. **T. Choi:** None. **S. Jeong:** None. **Y. jeong:** None. **C. Lee:** None. **K. Kim:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.08/G3

Topic: A.07. Development of Neural Systems

Support: PAPIIT Grant IN215725
SECIHTI CVU 517866
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Technical Support Moisés Mendoza Baltazar
Technical Support Natalia Moreno
Technical Support Nydia Hernández Ríos
Technical Support Beatriz Adriana García Frías

Title: Maternal gut dysbiosis induced by prenatal antibiotic exposure disrupts offspring myelination and behavioral development

Authors: *A. COLOM CASASNOVAS[1], O. ROJANO[1], F. VALDEZ-PALOMARES[4], B. PALACIOS-GONZALEZ[4], R. NAMBO[5], A. FALCÓN ALCÁNTARA[1], N. OCHOA RAMÍREZ[6], J. ORTIZ[2], D. GASCA-MARTINEZ[3], E. GARAY[1], R. ARELLANO OSTOA[1], A. CISNEROS-MEJORADO[2];
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Abstract: The maternal gut microbiota plays a critical role in brain development. Emerging evidence suggests that alterations in pregnancy-associated maternal gut microbiota (dysbiosis) may disrupt neurodevelopmental processes, leading to long-term changes in brain function. Within the gut-brain axis framework, dysbiosis has been associated with disorders involving altered myelinostasis, including autism spectrum disorder, depression and multiple sclerosis. However, the contribution of maternal dysbiosis during gestation to offspring myelin development remains unclear. In this study, we investigated the impact of maternal dysbiosis on myelination and related behavioral outcomes in a mouse model. Dysbiosis was induced by administering two oral antibiotics (Abx: 205 mg/Kg amoxicillin and 51mg/kg azithromycin) to pregnant C57BL/6J mice during the mid-gestation (E8-E14). Myelination was quantified at 2-, 4-, and 7- week-old offspring (Abx, n=8 and Control, n=9) using Black Gold II staining (BGII), while longitudinal analysis with diffusion-weighted magnetic resonance imaging (dMRI) was conducted by computing fractional anisotropy (FA) to infer microstructural changes; in addition, magnetic resonance spectroscopy (MRS) was used to explore key brain metabolites in the prefrontal cortex. dMRI analysis revealed FA decreases in prefrontal cortex, which correlates with histological BGII observations like a reduced prefrontal cortex myelination at different postnatal weeks. Also, we explored metabolite profiles in the prefrontal cortex, including NAA, Choline, creatine and GABA, indicative of brain integrity and myelin-related membrane

turnover. Neurobehavioral assessments (surface righting reflex, open field, elevated plus maze, and rotarod) revealed atypical motor responses, increased stereotypic behaviors in the open field ($p < 0.05$), and reduced time spent in the open arms of elevated plus maze, indicative of heightened anxiety-like behavior. Moreover, fecal samples from control and Abx-treated dams were collected before and after Abx exposure and subjected to 16S rRNA sequencing, which revealed significant alterations in microbial genera composition indicative of Abx-induced maternal gut dysbiosis. Our findings demonstrate that gestational Abx exposure alters neurodevelopmental behaviors correlating with the prefrontal cortex hypomyelination in offspring. These results suggest Abx-induced microbial restructuring may alter metabolites production associated with offspring myelination, supporting the role of the gut-brain axis in neurodevelopment. Further studies are required to elucidate the underlaying mechanisms.

Disclosures: A. Colom Casasnovas: None. **O. Rojano:** None. **F. Valdez-Palomares:** None. **B. Palacios-Gonzalez:** None. **R. Nambo:** None. **A. Falcón Alcántara:** None. **N. Ochoa Ramírez:** None. **J. Ortiz:** None. **D. Gasca-martinez:** None. **E. Garay:** None. **R. Arellano Ostoa:** None. **A. Cisneros-Mejorado:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.09/G4

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: BrightFocus Foundation A2023017S

Title: Oligodendroglia Regeneration as a Therapeutic Approach for TDP-43 Proteinopathies

Authors: F. MAYRHOFER[1], D. WARNER[2], C. SADEGH[3], ***O. CHECHNEVA**[4]; [1]Neurolog. Surgery, UC Davis, Sacramento, CA; [2]UC Davis, Davis, CA; [3]Neurosurg., [4]UC Davis, Sacramento, CA

Abstract: Accumulation and propagation of pathological proteins in neurons underlie the pathology of many genetic and age-related neurodegenerative disorders that affect memory, cognition, and movement, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease. Until recently, research on pathogenic protein aggregation has focused primarily on neurons. However, glial cells also express pathological proteins, leading to functional alterations that contribute to disease progression. TAR DNA-binding protein 43 (TDP-43) is a nuclear RNA-binding protein involved in multiple aspects of RNA metabolism. Cytoplasmic aggregation of TDP-43 has been documented in both neurons and oligodendroglia and is associated with loss of TDP-43 function and cell death, hallmark pathological features of ALS and FTD. While neurons have limited regenerative capacity, oligodendroglia retain a substantial ability to regenerate, making them an attractive therapeutic target. We hypothesized that oligodendroglia dysfunction driven by TDP-43 pathology

contributes significantly to disease manifestations and that restoration of oligodendroglial function may promote functional recovery. To test this hypothesis, we generated doxycycline-inducible transgenic mice expressing a mutant human TDP-43 lacking a nuclear localization sequence (hTDP-43-ΔNLS) specifically in Sox10-lineage oligodendroglia. Expression of this TDP-43 mutation in neurons has previously been shown to produce motor dysfunction resembling that observed in ALS. In our model, expression of hTDP-43-ΔNLS in oligodendroglia resulted in cytoplasmic translocation of TDP-43 and severe motor dysfunction. Remarkably, withdrawal of doxycycline led to significant functional recovery. Together, these findings demonstrate that oligodendroglia play a critical role in the pathogenesis of TDP-43 proteinopathies and highlight oligodendroglia regeneration as a promising therapeutic strategy for these disorders.

Disclosures: F. Mayrhofer: None. **D. Warner:** None. **C. Sadegh:** None. **O. Chechneva:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.10/H1

Topic: B.09. Glial Mechanisms

Support: NIH Grant 5U01NS136401-02

Title: Glia Architecture in the Mouse Optic Nerve, Chiasm, and Tract

Authors: M. BEAN[1], T. REESE[2], *A. MASELLI[3], N. B. KASTHURI[4], G. WILDENBERG[5]; [1]Dept. of Neurobio., The Univ. of Chicago, Chicago, IL; [2]Chicago State Univ., South Holland, IL; [3]Chicago State Univ., Chicago, IL; [4]Neurobio., Univ. of Chicago, Chicago, IL; [5]Neurobio., Univ. of Chicago Dept. of Neurobio., Chicago, IL

Abstract: Precise axon organization underlies neural circuit formation and function, yet the glial architecture supporting mature axonal circuits remains incompletely defined. The optic nerve, chiasm, and tract (ON-OT) system is an ideal model for studying axon organization, consisting primarily of retinal ganglion cell (RGC) axons traversing a densely populated glial environment in one direction, without synaptic connectivity along their length. Prior studies have identified glial subtypes within the ON-OT system, including astrocytes, oligodendrocytes, and microglia, and implicated glial-associated mechanisms in supporting RGC axon myelination, metabolic homeostasis, and circuit maintenance, yet their spatial distributions across ON-OT regions remain poorly defined. Here, we generate a spatial characterization of glial organization using immunofluorescence imaging of cryosectioned adult mouse ON-OT tissue and further validate our findings with volumetric electron microscopy. DAPI staining reveals anisotropic arrangement of nuclei in the optic nerve, but not at the chiasm or tract. Immunolabeling of glial subtypes reveals distinct morphological characteristics: oligodendrocytes organized as “beads-on-a-string” rows, and astrocytes and microglia with highly arborized processes, each with

anisotropic orientation distributions that are unimodal in the optic nerve and tract, and bimodal in the chiasm. At higher resolution, segmentation and 3D reconstruction of glial cells confirms the morphological signatures described above. Together, these findings provide a spatial characterization of glial organization in the adult mouse ON-OT system that establishes a structural basis for future work in models of development, disease, and injury.

Disclosures: M. Bean: None. **T. Reese:** None. **A. Maselli:** None. **N.B. Kasthuri:** None. **G. Wildenberg:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.11/H2

Topic: A.07. Development of Neural Systems

Support: NIH 1R21DA064062-01

Title: Deconvolution of gene regulation in microglial-dopaminergic neuronal interaction during striatal development

Authors: G. NDIWARI[1], O. OLABANJO[1,2], *P. LEE[1];
[1]Mathematics, Morgan State Univ., Baltimore, MD; [2]Dept. of Information Systems and Supply Chain Mgmt., Howard Univ., Washington DC, MD

Abstract: The coordinated development of dopaminergic neurons and microglia is essential for striatal maturation and functional circuit formation. Although numerous studieshave characterized individual cellular populations during development, the regulatory mecha-nisms linking neuronal differentiation, microglial maturation, and metabolic adaptation remainincompletely understood. Recent advances in single-cell transcriptomics provide an opportunityto reconstruct developmental gene regulatory networks at cellular resolution.Aim: This study aimed to deconvolute gene regulatory programs underlying microglial anddopaminergic neuronal development in the striatum and to identify shared transcriptional andmetabolic mechanisms governing cellular maturation.
An integrated developmental mouse striatal atlas comprising 128,511 cells and 2,000 highly variable genes was analyzed. Cell populations included direct-pathway spiny projection neurons (dSPNs), indirect-pathway spiny projection neurons (iSPNs),microglia, and other developmental cell types. Differential expression analysis, transcriptionfactor correlation analysis, developmental trajectory assessment, and regulatory subnetworkreconstruction were performed. Trem2-, Drd1-, and Drd2-centered subnetworks were recon-structed using high-expression cellular states. Candidate upstream regulators were identifiedusing Spearman correlation analysis, while metabolic associations were evaluated through cor-relations with Slc2a1, Hk2, Epas1, and Ddit4l.
The developing striatum is governed by three coordinated regulatory programs: a Foxp1 -driven

direct-pathway neuronal program, an Nfkbia-driven indirect-pathwayneuronal program, and a Trem2-centered microglial maturation program. The opposing rela-tionships between Drd2, Trem2, and Ddit4l suggest that metabolic adaptation constitutes akey regulatory mechanism linking neuronal differentiation and microglial activation during striatal development. These findings provide a systems-level framework for understanding cellularcoordination within the developing striatum.

Disclosures: G. Ndiwari: None. **O. Olabanjo:** None. **P. Lee:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.12/H3

Topic: A.06. Developmental Disorders

Support: State University of New York Empire Innovation Program

Title: Prenatal Alcohol Exposure Alters Microglia Complexity and Cortical Thickness in the Fetal Mouse Brain

Authors: *T. DORMAN, S. LAGUE, G. NOBLE, K. BOSCHEN;
Upstate Med. Univ., Syracuse, NY

Abstract: Fetal Alcohol Spectrum Disorders (FASD) encompasses a range of neurodevelopmental disorders, with neuroinflammation thought to be a major contributor to the associated pathologies. Microglia, the resident immune cells of the brain, are essential for proper neurogenesis, and prenatal perturbations to microglia can have significant neurodevelopmental consequences. Although embryonic microglia are known to respond to injury, it is unknown how prenatal alcohol exposure (PAE) influences their development and interaction with the developing CNS. This study investigates how PAE targeting microglia colonization alters their developmental trajectory and function during corticogenesis. Pregnant C57BL/6J mice were administered a single i.p. injection of alcohol (2.9 g/kg) or vehicle on embryonic days (E) 11-13, coinciding with peak microglia colonization. Brains from fetuses were dissected and imaged on E14 when the initial wave of microglia differentiation is thought to begin. Half of the litter was collected for cortical gene expression analysis (RT-qPCR), and the other half for immunohistochemistry. PAE significantly decreased cortical width ($p=0.03$) and length ($p=0.0059$) and was associated with significant changes in inflammatory gene expression. Microglia morphology was assessed as shape is dynamic in response to inflammation and can be correlated with cytokine production. Iba1+ microglia were analyzed in the hippocampus, paraventricular nucleus (PVN), and cortex, as these regions have high microglia densities and are associated with FASD. Microglia were categorized into 5 morphological classes: 1) round (large somas and no extensions), 2) stout (large somas and simple primary processes), 3) reactive (large somas and thick processes), 4) ramified (thin soma and many thin primary and secondary

processes), and 5) elongated rod (soma that is of equal width as its primary processes). Interestingly, alcohol significantly increased the complexity of microglia (p=0.04) in the PVN, inducing morphologies associated with mature, homeostatic function rather than activation. In the hippocampus, there is a significant increase in microglia density (p=0.4). These data suggest that PAE alters the development of microglia, influencing quantity and complexity in a region-dependent manner. Assessment of Iba1+ and TUNEL co-labeling revealed that microglia localized with apoptotic cells in the PAE brain, supporting a functional role for these cells. Future studies aim to determine if microglia morphological alterations lead to functional differences that could influence the observed cortical deficits.

Disclosures: T. Dorman: None. **S. Lague:** None. **G. Noble:** None. **K. Boschen:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.13/H4

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

Title: Age dependent responses of capillaries and microglia to LPS

Authors: *L. E. FREMUTH[1,2], M. DOCETI[3], A. LOPEZ[3], U. B. EYO[3];
[1]Neurosci., Univ. of Virginia Sch. of Med., Charlottesville, VA; [2]Cardiovasc. Res. Ctr., [3]Univ. of Virginia, Charlottesville, VA

Abstract: Neurovascular dysfunction is a shared feature of inflammatory, and neurodegenerative disorders, yet how immune challenges differentially impact the neurovasculature with age versus adulthood remains poorly understood. Capillary-associated microglia (CAMs) are uniquely positioned to influence capillary structure, cerebral blood flow, and blood-brain barrier (BBB) integrity, but whether their responses to inflammation are age dependent is unknown.Here, we use longitudinal *in vivo* two-photon imaging to define capillary and microglial responses to systemic lipopolysaccharide (LPS) in adulthood and aging. High-dose LPS induces rapid microglial activation accompanied by increases in capillary diameter, CAM density, and BBB permeability, with another repercussion being ablated hypercapnic capillary response. Aged mice exhibit blunted capillary phenotypes but prolonged BBB leakage. Longitudinal imaging reveals that both capillary and CAM phenotypes persist for days following acute inflammation, with the magnitude and duration of these responses diverging by age.Ongoing analyses extend these findings to include age-specific effects on red blood cell flux, microglial identity, and BBB structural integrity. Together, these data demonstrate that acute systemic inflammation elicits durable, age-dependent neurovascular and microglial responses.These findings suggest that aging fundamentally alters microglia-capillary coupling following immune challenge and may contribute to differential vulnerability to neurovascular dysfunction across the lifespan. Ongoing and future studies testing the role of microglial signaling pathways, such as those intersecting the

fields of aging, Alzheimer disease and inflammation, in regulating these interactions will help identify mechanisms linking inflammation, aging, and neurovascular disease.

Disclosures: L.E. Fremuth: None. **M. Doceti:** None. **A. Lopez:** None. **U.B. Eyo:** None.

Poster

PSTR042: Mechanisms of Glial Cell and Vascular Biology in Development and Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR042.14/H5

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

Support: K99R00 NS133298
T32 GM144636

Title: Glial Croquemort (SCARB2/CD36) is a key mediator of targeted synapse elimination across the lifespan

Authors: S. FEENEY[1], M. MICAEL[2], ***T. JAY**[1];
[1]Univ. of Iowa, Iowa City, IA; [2]Neurosci., UCSD, San Diego, CA

Abstract: While it has been established that glia play critical roles in regulating synapse development, we are still working to understand the rules that govern when and which synapses are formed and eliminated and how those rules are enforced at the cellular and molecular level. To identify the breadth of glial molecules that mediate synapse development, we performed an *in vivo* genetic screen using *Drosophila*. Out of 971 genes tested, we identified 48 genes that are required in glia for normal synapse development, the largest category of which were immune-related genes. This includes the scavenger receptor Croquemort (Crq), an ortholog to mammalian SCARB2 and CD36. We found that knockdown of Crq in glia disrupts developmental synapse elimination, specifically within excitatory and neuromodulatory, but not inhibitory synapses. This resulted in increased seizure susceptibility. We also found that loss of Crq in glia prevented age-related reductions in synaptic protein levels, suggesting Crq underlies a shared mechanism by which glial engage in synapse removal across the lifespan. Work is now ongoing to identify the neuronal ligands for Crq, with the goal to identify how those ligands are regulated to mark specific synapses for elimination in development and aging. We are also working to understand how Crq interacts with other immune molecules identified in the screen, and how peripheral immune pathways intersect with these central immune processes, to coordinate the processes of synapse development and maintenance.

Disclosures: S. Feeney: None. **M. Micael:** None. **T. Jay:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.01/H6

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

Support: Office of Undergraduate Research Supply Grant
Office of Undergraduate Research Fellowshio
Iowa Neuroscience Institute Summer Fellowship
Catalyst Grant from the Fraternal Order of Eagles Diabetes Research Center (FOEDRC) at the University of Iowa (A.S.)

Title: Sex-dependent regulation of the Dopamine Transporter (DAT) by insulin

Authors: *N. FASSETT[1], A. MELSON[1], B. A. POWERS[1], J. NEUHARTH[3], A. STEWART[2]; [1]Neurosci. and Pharmacol., [2]Univ. of Iowa, Iowa City, IA; [3]The Univ. Of Iowa Neurosci. Grad. Program, Iowa City, IA

Abstract: Obesity affects over 70% of U.S adults over the age of 20. Weight gain in obesity results from maladaptive food consumption irrespective of homeostatic needs. Though the prevalence of obesity is similar between sexes, women are more likely to develop severe obesity (BMI > 35) suggesting that biological sex may influence compulsive eating. Obesity has been linked to altered activity in dopamine (DA)-regulated brain circuits, which play key roles in motivation, reinforcement learning, and habit formation. The dopamine transporter (DAT) is the chief determinant of synaptic DA availability and exposure to obesogenic diets high in fat and sugar has been shown to impair DA clearance in the nucleus accumbens (NAc). However, prior work excluded female subjects and failed to systemically control for diet composition. We have now shown that high fat diet (HFD) feeding does not alter baseline DAT activity, pointing to sugar consumption as an influencing factor of DA clearance. Insulin is released as blood glucose rises following a meal and is known to be actively transported across the blood-brain barrier. Single cell nuclear RNA seq confirmed that insulin receptors (IRs) are expressed in DA neurons in rodents and humans, and insulin has been shown to increase DAT-driven DA uptake in vitro. We now demonstrate that insulin (1nM) increases uptake of [3H] DA in male ex vivo brain slices containing dorsal striatum (DStr), but not NAc or prefrontal cortex (PFC). However, this effect of insulin was absent in the DStr of females. Remarkably, chronic inhibition of nuclear progesterone receptors (PGRs) with mifepristone restored insulin-dependent DAT regulation in the female DStr. Our data demonstrate that the ability of insulin to modulate DAT is a sex- and region-specific and under hormonal control in females. Ongoing work seeks to establish the molecular basis for insulin- and progesterone-dependent DAT regulation and the impact of these mechanisms on food-driven habits. Ultimately, this work will yield valuable insights into how maladaptive changes in DAT function drive compulsive eating in individuals with obesity in a sex-biased manner.

Disclosures: N. Fassett: None. **A. Melson:** None. **B.A. Powers:** None. **J. Neuharth:** None. **A. Stewart:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.02/H7

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

Support: NIH Grant 1R21DA060410 (A.S.)
We thank Dr. Randy Blakely for generously providing the DAT Val559 C57BL/6 line

Title: Two is better than one: sex, strain, and gene dosage shape psychostimulant-driven behavior in DAT Val559 mice

Authors: *J. A. BERNHOLTZ;
Dept. of Neurosci. and Pharmacol., Univ. of Iowa, Iowa City, IA

Abstract: Disruptions in dopaminergic neurotransmission are implicated in multiple neuropsychiatric disorders most of which display pronounced sex bias in prevalence, age of onset, symptomology, and sensitivity to available therapeutics. Murine models expressing neuropsychiatric-disease associated variants in the dopamine (DA) transporter gene (DAT, *SLC6A3*), such as the Ala559Val substitution, have provided a platform to investigate the impact of sex on neurophysiology and behavior in a construct-valid model. The DAT Val559 mutation, identified in individuals with attention deficit/hyperactivity disorder (ADHD), bipolar disorder (BPD), and autism spectrum disorder (ASD), triggers anomalous DA efflux leading to ongoing disruptions in DA homeostasis. Previous studies have evaluated phenotypes of DAT Val559 homozygotes (HMZ) on a mixed background (~80% 129S6, 20% C57BL/6) despite the lack of evidence for biallelic DAT Val559 carriers in the human population. Here, we characterize the genetic penetrance of the DAT Val559 mutation in mice on a congenic C57BL/6 background. Consistent with prior studies, male HMZ mice exhibit blunted amphetamine (AMPH)-induced locomotion relative to WT controls, a phenotype absent in heterozygote (HET) males and HMZ females. HET females, conversely, exhibit increased sensitivity to the locomotor stimulating effects of AMPH. Cocaine-driven hyperactivity is also blunted in HMZ males relative to WT controls, a phenotype shared by male HETs. However, unlike results obtained using mixed background HMZ females, which lack cocaine-dependent locomotor activation, HMZ females on the C57BL/6 background demonstrated elevated distance travelled following cocaine treatment as compared to WT controls. Finally, whereas DAT Val559 genotype has minimal impact on baseline locomotion, we noted striking changes in thigmotaxis in HET mice that were absent in HMZ animals. More specifically, HET males exhibited dramatically reduced center occupancy in the open field compared to WT controls irrespective of drug exposure. HET females, in contrast, spent more time in the center relative to their WT and HMZ littermates, a phenotype rescued by AMPH. Together, these data demonstrate that genetic background and sex modify the phenotypic impact of the DAT Val559 mutation. Notably, novel phenotypes were observed in HETs that are absent in HMZs mice raising the intriguing possibility that the presence of the DAT Val559 mutant may impede or alter functionality of WT DAT. Ongoing work seeks to evaluate sex-, region-, and genotype-dependent alterations in DAT activity as well as the downstream impacts on dopaminergic circuit function and behavior.

Disclosures: J.A. Bernholtz: None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.03/H8

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

Support: NIH Grant 1R21DA060410
NIH Predoctoral Traning Grant T32 GM144636

Title: D2 Autoreceptors Regulate the Dopamine Transporter in a Sex- and Region-Dependent Manner

Authors: *B. A. POWERS[1], N. FASSETT[1], J. BERNHOLTZ[1], D. LIU[2], J. I. NEUHARTH[2], A. STEWART[1];
[1]Neurosci. and Pharmacol., [2]Interdisciplinary Grad. Program in Neurosci., Univ. of Iowa, Iowa City, IA

Abstract: Dysregulation of dopaminergic neurotransmission has been linked to numerous neuropsychiatric disorders, virtually all of which display a sex bias in prevalence, age of onset, and/or clinical symptomology. The presynaptic dopamine (DA) transporter (DAT), the primary facilitator of rapid synaptic DA clearance, is essential for maintenance of DA homeostasis. DAT is controlled by several regulatory mechanisms including an important negative feedback loop mediated by D2-type DA autoreceptors (D2ARs), which, when activated, increase surface trafficking of DAT to aid in the inactivation of synaptic DA. Previous work has identified sex-biased and region-specific coupling between DAT and D2AR wherein D2AR-dependent DAT threonine 53 (T53) phosphorylation and membrane trafficking occur exclusively in the nigrostriatal DA circuit in male mice but are only observed in the mesolimbic DA circuit in females. However, it remains unclear how or if changes in DAT phosphoregulation or surface expression translate into alterations in DA clearance. To functionally assess the impact of D2ARs on DAT mediated DA reuptake, we isolated brain slices containing dorsal striatum (DStr), nucleus accumbens (NAc) and pre-frontal cortex (PFC), projection regions defining the three major DA circuits, from both male and female WT C57BL/6 mice and performed ex vivo [^{3}H] DA uptake assays following bath application of the D2/D3 agonist quinpirole or D2/D3 antagonist sulpiride. Our results show that quinpirole exerts a concentration-dependent effect on DAT function specific to the male DStr. More specifically, low dose quinpirole (0.1 μM) resulted in a significant decrease in DA uptake and a higher concentration (1 μM) led to a significant increase in DA uptake. Interestingly, quinpirole failed to impact DA uptake in the NAc or PFC of males or in any of the assessed female projection regions. Sulpiride treatment also inhibited DA uptake exclusively in the male DStr. The lack of autoreceptor dependent feedback driving enhanced DA reuptake in females is predicted to dramatically shape DA dynamics in vivo and highlights a disconnect between DAT phosphorylation state, surface

expression, and transporter function. Ongoing work utilizes a novel tamoxifen inducible D2AR knockout mice (Drd2$^{flx/flx}$:DATiCreER) to evaluate the in vivo consequences of differential autoreceptor action between the sexes on DA release and reuptake as well as animal behavior. Importantly, we hypothesize that sex biased D2AR-DAT coupling might represent a key mechanism determining sex specific susceptibility to neuropsychiatric disorders many of which have been linked to DA dysregulation.

Disclosures: B.A. Powers: None. **N. Fassett:** None. **J. Bernholtz:** None. **D. Liu:** None. **J.I. Neuharth:** None. **A. Stewart:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.04/I1

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

Support: NIH, NIDDK Intramural Grant ZIADK031117
NIH, NIDDK Intramural Grant ZIADK031127
FDA CDER-20-I-0546
DEA D-22-OD-0001
NIH, NIDA Extramural Grant ADA12013

Title: Nucleoside Modulators of Human Monoamine Transporters: Bitopic Stabilization Enables Triple Inhibition

Authors: *K. A. JACOBSON[1], M. PAVAN[1], L. B. KOZELL[2], A. J. ESHLEMAN[3], J. SCHMACHTENBERG[4], K. WOLFRUM[5], W. SCHUTZER[4], A. I. ABBAS[6], D. K. TOSH[7]; [1]NIDDK, NIH, Bethesda, MD; [2]Psychiatry, Oregon Hlth. & Sci. Univ., Portland, OR; [3]Psychiatry and Beh Neuroscience, OHSU, Portland VAMC, Portland, OR; [4]Oregon Hlth. and Sci. Univ., Portland, OR; [5]VAMC, Portland, OR; [6]Dept. of Behavioral Neurosci., Vaporhcs/Oregon Hlth. & Sci. Univ., Portland, OR; [7]NIDDK, Natl. Institues of Hlth., Bethesda, MD

Abstract: A recently reported human dopamine transporter (hDAT) cryo-EM structure was stabilized by an allosteric inhibitor, i.e. a rigidified North (N)-methanocarba-adenosine analogue MRS7292 **1**, tropane orthosteric inhibitor (β-CFT) and Zn^{2+}. The position of the nucleoside defined a previously unknown allosteric monoamine transporter (MAT) site. MRS7292's pharmacological profile was unusual, i.e. increasing tropane radioligand affinity, while inhibiting dopamine transport. Here, we have synthesized analogues of **1**, with N^6, C2 and 4' modifications to examine their effects on radioligand binding at DAT (either enhancement like **1**, or newly detected inhibition) and at the norepinephrine (NET) and serotonin (SERT) transporters (inhibition only), and uptake. Small N^6 groups, i.e. N^6-methyl (e.g. MRS7232) and N^6-cyclopropyl (e.g. MRS8462) analogues, provided the pronounced DAT enhancement, e.g.

≥500% of control at 10 μM, especially with 5'-ethyl ester or N^6-methyl-4'-cyanomethyl (e.g. MRS8406) functionality. 4'-Cyanomethyl functionality, but not 4'-cyano, strongly promoted either radioligand enhancement or inhibition, depending on other substituents. Molecular dynamics simulation predicted π-π interactions of a N^6-(ω-phenyl-alkyl) substituent with aromatic side chains of $F208^{EL2}$ and $H375^{EL4}$ (aromatic conserved at NET) to define a preferred binding mode for N^6-extended chains at all MATs. Thus, the phenyl rings of extended N^6-(5-phenylpentyl) and N^6-(6-phenylhexyl) groups of bitopic ligands engage predicted distal aromatic interactions at a previously undetected site. The core nucleoside position remained like **1**. N^6-(6-Phenylhexyl)-2-iodo compounds inhibited DAT binding (e.g. MRS8456, 5'-hydroxy, K_i 0.89 μM, a pan-inhibitor; and MRS8455, 4'-cyanomethyl, K_i 0.40 μM). Thus, inactivity of C2-iodo analogues (i.e. missing the rigid, extended C2-arylethynyl group of **1**) could be compensated by elongated N^6 groups. Chiral N^6 groups displayed binding stereoselectivity. In summary, we characterized the MAT structure activity relationship of this series, either enhancement or inhibition of orthosteric radioligand binding, and transport inhibition, and revealed detailed structural predictions.

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Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.05/I2

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

Support: R01DA023205 (C.R.M.)
Z1A DA000103-26 (J.L.K.)
Butler University Holcomb Research Award (W.C.H)

Title: Pharmacological and biochemical studies on dual sigma-1 and dopamine transporter ligand WA241

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Abstract: Currently there are no FDA-approved drugs for treating cocaine addiction. Recently we reported the preclinical profile of CM699, a dual inhibitor of sigma receptors (Sigma-R) and the dopamine transporter (DAT) (Hiranita T, Hong WC, Sharma A, et al. *ACS Chem Neurosci*. 2025;16(8):1454-1468). WA241 is an analog of CM699 that was generated by the addition of a

fluorine atom to increase lipophilicity and slow metabolism. In radioligand binding experiments WA241 exhibited K_i values of 2.18 nM and 301 nM for Sigma1-R and the DAT, respectively. WA241 had a longer $T_{1/2}$ than CM699 (55 min vs. 13 min) in human live microsomal metabolic stability studies. In a biochemical method assessing multimerization of Sigma1-R, WA241, similar to CM699, increased Sigma1-R multimers detected in nondenaturing protein gels. In contrast, the Sigma1-R agonist, (+)-pentazocine, decreased Sigma1-R multimers. Additionally, WA241 blocked the effects of (+)pentazocine, confirming it as an antagonist at Sigma1-R. We further probed DAT conformational changes using cysteine accessibility assays in cell models co-expressing DAT and Sigma1-R. Unlike the typical DAT inhibitor cocaine, WA241 did not affect cysteine accessibility of DAT transmembrane domain 6a (TM6a). The Sigma1-R agonist (+)-pentazocine potentiated cocaine-induced cysteine accessibility of DAT TM6a, suggesting that it facilitated a shift towards the outward-facing conformation of DAT, whereas WA241 appeared to block this effect of (+)pentazocine. These data are consistent with the hypothesis that WA241 possesses dual actions as a sigma1-R antagonist and an atypical DAT inhibitor, and future studies are necessary to explore its potential to mitigate cocaine self-administration in animal models.

Disclosures: W.C. Hong: None. **A. Sharma:** None. **W. Alsharif:** None. **J.L. Katz:** None. **C.R. McCurdy:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.06/I3

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

Support: 1R01ES035518-01A1
4T32MH064913-14
1T32GM149371-01

Title: A Tyrosine Hydroxylase-Specific Condition Knockout of SVCT2 Isolates the Catecholaminergic Consequences of Ascorbate Deficiency

Authors: *R. L. JONSCHER[1], K. COOKE[2], N. AREGBE[2], F. HARRISON[2];
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Abstract: Ascorbic acid (ASC; vitamin C) is an essential micronutrient. An estimated 10-20% of people experience ASC depletion or deficiency, with increased rates among psychiatric populations. These patients are frequently prescribed drugs that target catecholamine systems, as is the case for attention deficit hyperactivity disorder (ADHD). Beyond its antioxidant properties, ASC regulates catecholamine synthesis through epigenetic regulation of biosynthetic genes, reductive stabilization of the tyrosine hydroxylase (TH) cofactor tetrahydrobiopterin, and by

serving as the obligatory cofactor for dopamine-β-hydroxylase. Murine models of ASC deficiency show suppressed motor function and cognitive dysregulation linked to decreased striatal dopamine. These models disable ASC synthesis via knockout (KO) of gulono-L-lactone oxidase or transport via KO of sodium-dependent vitamin C transporter 2 (SVCT2; Slc23a2). But both models non-specifically deplete brain ASC and carry potential developmental confounds. To isolate the specific role ASC plays in catecholamine synthesis and neurotransmissionsignaling, we generated a TH-specific, tamoxifen-inducible conditional KO of SVCT2 (TH-CreERXSlc23a2fl/fl). Preliminary immunohistochemistry and HPLC confirm decreased SVCT2 in TH+ neurons of the ventral tegmental area and lower ASC, dopamine, and norepinephrine in the adrenal gland. We ran a blinded behavioral battery 6 weeks post-induction (2-3 months old) in wild-type, heterozygous (HET), and KO mice of both sexes. All groups showed normal grip strength and weight gain. However, KO mice showed progressive reductions in open-field exploration. KO mice show deficits in motor coordination on the rotarod and decreased motivation in the tail-suspension test (TST). Following TST, KO and HET spent more time in the center of an open -field arena, suggesting suppressed stress-induced anxiety-like behavior. Fear conditioning indicated cue- and context-dependent associative memory deficits. Working memory, investigatory drive, prepulse inhibition, and shock perception were unchanged between groups. We therefore conclude that catecholamine-selective SVCT2 deletion elicits a hypodopaminergic phenotype, suggesting dopamine deficits in the striatum and hippocampus. HPLC will be used to assess catecholamines and their metabolites across brain areas. Dopamine release and uptake dynamics at baseline and in response to methylphenidate will be assessed using fast-scan cyclic voltammetry.

Disclosures: R.L. Jonscher: None. **K. Cooke:** None. **N. Aregbe:** None. **F. Harrison:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.07/I4

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

Title: Beyond Neurotransmission: Characterization of Histone Serotonylation Machinery in Serotonergic Neurons

Authors: *E. ESHOO;
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Abstract: Mood disorders such as Major Depressive Disorder (MDD) are a leading cause of disability in the United States and are strongly associated with alterations in serotonin (5HT) neurotransmission. First-line treatments, selective 5HT reuptake inhibitors (SSRIs), act by blocking the 5HT transporter (SERT) to prolong 5HT signaling. However, SSRIs achieve remission in only approximately 60% of patients and typically require at least two weeks to exert therapeutic effects. This delayed onset and limited efficacy, despite the rapid nature of

serotonergic neurotransmission, suggest that the traditional monoamine hypothesis may be insufficient to fully explain 5HT's role in mood regulation. Recently, a novel function for 5HT has emerged as a post-translational modifier of proteins, including histone H3, through a process known as serotonylation. Transglutaminase 2 (TGM2), a ubiquitously expressed GTPase, is thought to mediate the calcium-dependent covalent attachment of 5HT to histone proteins. Histone serotonylation has been demonstrated in cultured cells and detected in the dorsal raphe nucleus (DRN) of both humans and rodents, a brain region that houses the majority of serotonergic neurons. To better understand the cellular machinery underlying this process, we performed immunohistochemistry (IHC) and RNAscope analyses on rodent brain sections to characterize the expression of serotonylation-related components within the DRN. We examined whether TGM2 mRNA is expressed in serotonergic neurons by combining a TGM2 RNA probe with antibodies against SERT or tryptophan hydroxylase 2 (TPH2), the rate-limiting enzyme in 5HT synthesis. Preliminary findings indicate that TGM2 mRNA is present within serotonergic cell bodies in the DRN. We next investigated whether TGM2 protein expression mirrored these patterns by performing IHC with antibodies against TGM2 and SERT. In adjacent sections, 5HT immunostaining was used to assess the distribution of 5HT within the same region. These studies suggest that TGM2 and SERT are co-expressed within serotonergic cell bodies and that 5HT itself is localized to these neurons. Together, these findings indicate that key molecular components required for histone serotonylation, including TGM2 and 5HT, are present within serotonergic neurons of the DRN. Future studies will quantify the extent of co-localization among these factors and evaluate the functional relevance of this machinery in animal models of depression. Collectively, this work provides insight into a novel role for 5HT beyond classical synaptic neurotransmission and may advance our understanding of 5HT-dependent mechanisms involved in mood disorders.

Disclosures: E. Eshoo: None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.08/I5

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

Title: A Multi-Platform Strategy for Functional Characterisation of EAAT2

Authors: A. BIZIOR[1], E. MALONE[1], L. C. D. GIBSON[1], C. BROWN[1], *L. HUTCHISON[1], **G. CUCINIELLO**[2], N. BRYSON[1], J. KEWNEY[1];
[1]Sygnature Discovery, Glasgow, United Kingdom; [2]Sygnature Discovery, NOTTINGHAM, United Kingdom

Abstract: Excitatory amino acid transporters (EAATs) are essential for maintaining extracellular glutamate homeostasis and preventing excitotoxicity in the central nervous system. Among these, EAAT2 (SLC1A2) is the predominant glial transporter responsible for the majority of

synaptic glutamate clearance, making it a key therapeutic target in neurological disorders and cancer. However, scalable and physiologically relevant functional assays are required to support drug discovery efforts. Here, we present a multi-platform strategy for functional characterisation of EAATs, using EAAT2 as a primary model. We employed solid-supported membrane electrophysiology (SURFE2R) to measure substrate-induced electrogenic transport in membrane vesicles. This approach enables real-time, label-free detection of transporter activity through rapid solution exchange and ion gradient-driven current responses. Cross-platform validation of standard reference compounds, using complementary methods, including two-electrode voltage clamp, radiolabelled uptake, and fluorescence-based assays, confirmed the functional and pharmacological relevance of the system. Together, these findings establish a reliable and scalable platform for EAAT2 functional profiling, supporting high-throughput screening of EAAT-modulating compounds and enabling detailed downstream mechanistic analysis.

Disclosures: A. Bizior: None. **E. Malone:** None. **L.C.D. Gibson:** None. **C. Brown:** None. **L. Hutchison:** None. **G. Cuciniello:** None. **N. Bryson:** None. **J. Kewney:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.09/I6

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

Support: ZIA MH002946-13
NIH Intramural Research Program

Title: Scanning the C-terminus of Neuronal Glutamate Transporter EAAT3 for Sorting Nexin Binding Motifs

Authors: *O. PEMBERTON, S. RADHAKRISHNAN, S. G. AMARA;
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Excitatory amino acid transporter 3 (EAAT3) is a plasma membrane neurotransmitter transporter that is essential for clearing glutamate from the extrasynaptic space. The regulation of extracellular glutamate plays a crucial role in modulating neuronal signaling. EAAT3 mutations are linked to several neuropsychiatric disorders, including schizophrenia and obsessive-compulsive disorder. Drugs such as amphetamine and methamphetamine regulate EAAT3 surface expression, and mutations within a ^{504}VNGGF^{508} motif in the C-terminus of EAAT3 alter the membrane localization and amphetamine sensitivity. To investigate the regulation of EAAT3 trafficking, endogenous interactors and constitutive binding partners of EAAT3 were identified using a proximity labeling technique that identifies proteins within a 100 nm radius of EAAT3. Among the proteins enriched in proximity to EAAT3, we found proteins related to endosomal transport and retrograde transport. Two of these proteins were Sorting Nexin 3 (SNX3) and Sorting Nexin 17 (SNX17), which are involved in intracellular trafficking of cargo using the

retromer and retriever complexes, respectively. To confirm the interaction between EAAT3 and the sorting nexins, we performed colocalization studies in N2A cells and neurons using confocal microscopy and demonstrated that the two proteins interact at early endosomes using super-resolution STED microscopy. To investigate their effect on EAAT3 trafficking, we performed functional studies by knocking out the sorting nexins with short interfering RNAs and measured changes in EAAT3 surface expression with membrane biotinylation. Knocking out SNX3 results in increased surface expression of EAAT3, whereas knocking out SNX17 results in decreased surface expression of EAAT3. To determine the sites required for sorting nexin interactions, we mutated several residues within canonical SNX3 and SNX17 regulatory motifs in the C-terminus of EAAT3. We measured the effects these mutations have on EAAT3 surface expression using membrane biotinylation experiments and performed immunostaining to determine how the mutations reroute intracellular trafficking of EAAT3. Our preliminary experiments suggest the presence of a regulatory switch that determines how EAAT3 interacts with the different sorting nexins. We mutated a known phosphorylation site upstream of the SNX17 and SNX3 binding site, to examine whether this site regulates EAAT3 binding to either sorting nexin. Together, this helps us elucidate the constitutive regulation of EAAT3 by sorting nexins and will help us further understand how amphetamines regulate EAAT3 trafficking and glutamatergic signaling.

Disclosures: O. Pemberton: None. **S. Radhakrishnan:** None. **S.G. Amara:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.10/I7

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

Support: PRIN2022BZWEKA
NIH R56NS12955601
Age-It PE0000015/F33C2200049006

Title: A Quantitative Analysis of GLT-1 Localization at Cortical GABAergic Synapses

Authors: *M. MELONE[1,2], M. DI PALMA[1], A. SCIMEMI[3], F. CONTI[1,4];
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Abstract: Extracellular glutamate that escapes from excitatory release sites enables excitatory-inhibitory crosstalk; however, the architecture of the main astrocytic glutamate transporter GLT-1 surrounding cortical inhibitory contacts remains poorly characterized. We employed quantitative pre-embedding electron microscopy for GLT-1 and the Na+/K+-ATPase α2 isoform, combined with post-embedding immunogold labeling, to map astrocytic leaflets (ALs) associated with morphologically identified symmetric synapses in rat and human cortex. In pre-

embedding material, GLT-1-positive (+) ALs were frequently observed adjacent to axo-somatic, proximal axo-dendritic, and distal axo-dendritic symmetric synapses; after distance-based phenotyping, 65.2% of symmetric synapses showed symmetric-associated GLT-1+ ALs. To differentiate inhibitory synapse-associated profiles from those primarily related to neighboring excitatory contacts, GLT-1- and α2+ ALs were analyzed using distance-based criteria relative to the symmetric synaptic edge and the nearest asymmetric synapse within the same ultrastructural field. This approach identified matched populations of symmetric synapse-associated GLT-1+ and α2+ ALs, with α2 paralleling GLT-1 in prevalence at symmetric synapses and in subtype-dependent geometry. In particular, distal axo-dendritic contacts exhibited shorter leaflet-to-synaptic-edge distances and a tighter local asymmetric synaptic neighborhood. Post-embedding immunogold labeling confirmed that membrane-associated GLT-1 is extrasynaptic relative to symmetric synapses (thus, over 300 nm from the edges of synaptic contacts) and preferentially enriched near distal inhibitory contacts. Double immunogold labeling further revealed that GLT-1/α2 membrane pairs with an interdistance ≤50 nm were more frequently located within 1000 nm of distal than proximal symmetric synaptic edges in rat cortex (81.3% vs. 30.8%); this distal enrichment was also evident in human cortex (73.5% vs. 38.1%). These results indicate that GLT-1 and α2 exhibit matched, subtype-dependent astrocytic organization at cortical symmetric synapses, delineating transporter-associated membrane microdomains that may influence glutamate spill-in and glutamate-dependent modulation of inhibitory transmission.

Disclosures: M. Melone: None. **M. Di Palma:** None. **A. Scimemi:** None. **F. Conti:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.11/I8

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

Support: CVU: 2068622

Title: Blue light induces early dysregulation the sodium-dependent glutamate transport in retinal Müller cells through p38 MAPK activation

Authors: *N. MORALES-RAMÍREZ[1,2], L. C. HERNANDEZ[2], E. CALDERON-ARANDA[2], E. LOPEZ-BAYGHEN[2], A. ORTEGA[2];
[1]Ctr. de Investigacion y Estudios Avanzados del Inst. Politécnico Nacional, Mexico, Mexico; [2]Toxicología, Cinvestav-IPN, Mexico City, Mexico

Abstract: The fast expansion of LED-based lighting and digital displays has increased human exposure to blue light. This issue is particularly important in children who are exposed to LED-based screens from early ages. In this population, a more transparent crystalline lens allows a greater proportion of short-wavelength light to reach the retina. Retinal development ends at an age of 7 years, increasing children susceptibility to blue light-induced damage. Although blue

light results in oxidative stress, mitochondrial dysfunction, and retinal injury, most work has focused on photoreceptors and pigment epithelial cells, whereas the impact on Müller glial cells remains unknown. Since Müller cells are central to retinal homeostasis through clearance of extracellular glutamate, an impaired glutamate uptake might precede neuronal dysfunction and excitotoxicity. In this study, we evaluated the effects of blue light on glutamate uptake activity and p38 MAPK activation in retinal Müller cells.Primary cultures of rat Müller cells were exposed to blue LED light under controlled conditions. Cell viability was assessed by MTT while glutamate transporter activity was evaluated by a [^{3}H]-D-Aspartate uptake, and p38 MAPK signaling was analyzed via Western blot of Tyr 182 p38 phosphorylation. Blue light induced significant changes in [^{3}H]-D-Aspartate uptake without substantial loss of viability, indicating that functional disturbances might occur before detectable neuronal death. Glutamate uptake displayed a biphasic pattern, with an initial increase followed by a diminution, accompanied by dynamic changes in p38 MAPK phosphorylation, consistent with an stress-responsive signaling. These findings indicate that blue light elicits early functional alterations in Müller cells, characterized by biphasic regulation of glutamate transport and p38 MAPK activation, and suggest that disruption of glutamate homeostasis may contribute to increased susceptibility to retinal degeneration.

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Poster

PSTR043: Neurotransmitter Transport and Degradation

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Program #/Poster #: PSTR043.12/J1

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

Support: ISN Career Development Grant
IBRO Rising Stars Award
Presidential Research Grant NSU

Title: From Genes to Function: A Systematic Review of the Regulation of xCT, the Cystine/Glutamate Antiporter

Authors: S. CHIRLA, R. PANDIT, *Z. MARTINEZ-LOZADA;
Psychology and Neurosci., Nova Southeastern Univ., Ft. Lauderdale, FL

Abstract: The cystine/glutamate antiporter, also known as system Xc-, is a sodium-independent, chloride-dependent, amino acid antiporter that imports the anionic form of cystine in exchange for glutamate with a 1:1 ratio. System Xc- is formed by two subunits linked by a disulfide bridge: a light chain, xCT (coded by the gene Slc7a11), and a heavy chain, CD98 (coded by the gene Slc3a2). The transport activity of system Xc- depends on the light chain xCT, while CD98 acts as a chaperone guiding and anchoring xCT to the plasma membrane. In the brain, system

Xc- has two critical roles: 1) imports cystine used to form glutathione (GSH), the most important antioxidant in the brain; 2) regulates the extracellular concentration of glutamate, the main excitatory neurotransmitter. The antioxidant function of xCT has been highlighted by the discovery of ferroptosis, a distinctive form of programmed cell death triggered by lipid peroxidation and the accumulation of reactive oxygen species, increasingly recognized as a driver of neuronal death in Alzheimer's, Parkinson's, and Huntington's disease. Additionally, numerous cancers overexpress xCT, correlating with worse outcomes. In glioblastoma, overexpression of xCT contributes to GSH-mediated drug resistance and facilitates tumor expansion. The mechanisms by which healthy cells regulate xCT expression, and whether different cancers employ identical molecular mechanisms to upregulate xCT, have not been systematically studied. To this end, we performed a systematic review of 122 publications identified via PubMed keyword searches for xCT, Slc7a11, and cystine/glutamate antiporter, and screened for mechanisms of expression regulation. The articles were categorized into six levels of molecular regulation: epigenetic, transcriptional, post-transcriptional, translational, post-translational, and protein-protein interactions/cell localization. We found that xCT is regulated at nearly all known levels of expression control, many activated in response to stress. Given xCT's central role in brain homeostasis, mechanistic insights from cancer research may offer additional clarity into the xCT dysregulation observed in brain pathologies and inform future therapeutic approaches.

Disclosures: S. Chirla: None. **R. Pandit:** None. **Z. Martinez-Lozada:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

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Program #/Poster #: PSTR043.13/J2

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

Support: NIH Grant R35-GM138023
NSF Grant Cooperative Agreement No. OIA-2242771

Title: The Discovery and Refinement of Small Molecule Compounds that can act as ZIP12 Agonists and Antagonists

Authors: *E. TRATE[1], R. MESTEMACHER-MCCLANAHAN[1], W. H. WALKER, II[1], C. T. ANDERSON[2];
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Abstract: Zinc is the second most common trace element in the body, and has numerous roles in maintaining homeostasis, immune function, and neurological processes. The auditory cortex is highly enriched with synaptic zinc, which is released from neurons and modulates cortical activity. Synaptic zinc in neurons arises from the action of the zinc transporter protein ZnT3, one

of 11 members of the ZnT family (Slc30a1-10 and TMEM163). The zinc transporter ZIP12, one of 14 ZIP members (Slc39), is expressed by astrocytes and contributes to zinc clearance from synapses in the brain. Current tools in the field for studying synaptic zinc include genetic knockout/knockdown approaches, zinc chelators, and manipulation of neuronal activity. However, ZIP12 has a largely unexplored role in affecting zinc levels at synaptic terminals in the brain, in large part due to a lack of targeted pharmacological agents to effectively study its function. Our lab has established a group of compounds called ZiMo that can affect the function of ZIP12 and modulate neuronal activity and synaptic signaling.
HEK293T cells were transfected by plasmid and by lentivirus to express ZIP12. These cells were used to assess the effects of ZiMo compounds on ZIP12 function. We used a fluorescence screening assay to quantify the potency and specificity of ZiMo compounds for different zinc transporters, and western blot analysis to determine expression.
We find that certain ZiMo compounds affected the zinc transporter ZIP12. The ZIP12-transduced lentiviral cells had higher amounts of zinc-induced intracellular zinc levels that can be altered by specific ZiMo compounds. This methodology is used to identify and refine ZiMo compounds specific for ZIP12 compared to other zinc transporter proteins.
Our results strongly support the advancement of ZIP modulators for use in neuroscience research, as well as the potential for transporter-specific modulation that could be used to advance zinc studies in other tissues and be used for targeted therapeutics.

Disclosures: E. Trate: None. **R. Mestemacher-McClanahan:** None. **W.H. Walker:** None. **C.T. Anderson:** None.

Poster

PSTR043: Neurotransmitter Transport and Degradation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR043.14/J3

Topic: C.01. Brain Wellness and Aging

Support: MJFF ASAP-025189
Chan Zuckerberg Initiative - DAF2021-237435
HHMI Investigator Fund (Cagla Eroglu)

Title: Gabapentin Receptor α2δ-1 controls Neuronal Nutrient-Dependent Endolysosomal Signaling via interacting with Huntingtin

Authors: *R. M. BAUMERT[1], N. BROSE[1], G. SEJOURNE[1], L. BRADLEY[1], S. U. MCKINSTRY[1], C. EROGLU[1,3,2];
[1]Cell Biol., [2]Neurobio., Duke Univ. Sch. of Med., Durham, NC; [3]Howard Hughes Med. Inst., Durham, NC

Abstract: How neurons sense amino acid availability to regulate endolysosomal function and synaptic proteostasis remains poorly understood. Here, we identify the synaptogenic receptor

α2δ-1 as an endosomal leucine sensor that couples amino acid availability to endolysosomal protein degradation and synaptic proteostasis in cortical neurons. Upon ligand engagement, α2δ-1 signals to nutrient-responsive signaling pathways, including mTORC1, to suppress endolysosomal degradation, whereas loss of α2δ-1 results in persistently elevated degradative activity. These findings reveal an unexpected role for α2δ-1 beyond its established function in synaptogenesis. We find that this nutrient-sensing function is executed via a previously unrecognized complex with Huntingtin (Htt), the protein whose N-terminal polyglutamine expansion underlies Huntington's disease (HD). Through molecular modeling and biochemical analyses, we mapped the Htt:α2δ-1 interaction to the N-terminal region of Htt and found that the HD-causing polyQ expansion impairs this interaction. Disruption of the Htt:α2δ-1 complex, by Htt point mutations at interaction residues or by polyQ expansion, impairs neuronal responsiveness to leucine and disrupts endosomal compartment positioning and organization, indicating that Htt is required for α2δ-1-mediated nutrient sensing. Together, our findings define a molecular pathway linking amino acid sensing to endolysosomal regulation and synaptic proteostasis through the Htt:α2δ-1 complex. Disruption of this pathway by HD-associated mutations provides a potential mechanistic link between altered nutrient sensing, endolysosomal dysfunction, and synaptic vulnerability in neurodegenerative disease.

Disclosures: R.M. Baumert: None. **N. Brose:** None. **G. Sejourne:** None. **L. Bradley:** None. **S.U. McKinstry:** None. **C. Eroglu:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

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Program #/Poster #: PSTR044.01/J4

Topic: B.05. Synaptic Plasticity

Support: NIH Grant MH135565
NIH Grant NS118440

Title: Should I stay or should I go: Morphological factors that predict neuronal persistence or cessation of involvement in dentate gyrus engrams

Authors: *K. O. MCDONALD[1], T. YU[2], L. VAN BOEKHOLDT[3], S. J. ATON[4];
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Abstract: Learning and memory involve network level changes in activity and connectivity between cells. Consolidation of many hippocampus-dependent memories - such as episodic memory - relies on post-learning sleep, although the mechanisms by which sleep influences memory formation are not completely understood. It has been hypothesized that neurons active during learning reactivate during post-learning sleep to stabilize the memory engram. Indeed, sleep-dependent engram neuron reactivation has been observed in the rodent hippocampus

following single trial learning tasks including contextual fear conditioning. In order to determine if engram neuron reactivation is associated with changes in spine density during active memory consolidation, we investigated the morphology of reactivating and non-reactivating engram neurons. To do this, we used TRAP2 fluorescent labeling of context -specific neuron populations in the mouse hippocampus. Mice then underwent single-trial contextual fear conditioning, followed by post-conditioning sleep or sleep deprivation. In congruence with previous reports, we find that sleep deprivation reliably reduces engram reactivation. In sleeping mice, we observed differences between dendritic spines on reactivated and non-reactivated engram neurons. Unexpectedly, reactivated engram neurons had lower thin spine density than non-reactivated engram neurons in mouse dentate gyrus. Future studies will address the sleep-dependence of this phenomenon, and how these dendritic spine changes relate to successful memory storage.

Disclosures: K.O. McDonald: None. **T. Yu:** None. **L. van Boekholdt:** None. **S.J. Aton:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.02/J5

Topic: B.05. Synaptic Plasticity

Support: 1R01HL142752
1R21HD112147

Title: Dendritic spine development in the nucleus accumbens of offspring exposed to gestational intermittent hypoxia

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Abstract: There is little knowledge on the extent to which maternal immune activation during gestation has long-term effects on offspring development and cognition. One of the most common disorders mothers can develop during pregnancy is sleep apnea (SA). Marked by recurrent cessation of breathing throughout sleep, SA causes fluctuations in blood oxygen levels inducing a state of gestational intermittent hypoxia (GIH). In a rat model of maternal GIH, previous work from our group identified a lack of pruning of medial prefrontal cortical dendritic spines (pyramidal neurons) spanning from childhood into adolescence. These spine alterations were associated with a constellation of behavioral aberrations, including social withdrawal, increased anxiety, repetitive behaviors, and cognitive deficits. Importantly, these neuronal and behavioral phenotypes were present in male, but not female, offspring. Emerging evidence in humans suggests that maternal sleep apnea during gestation is associated with adverse behavioral phenotypes in offspring. Despite these associations, lacking is knowledge of whether maternal

GIH affects dendritic spine development and formation in brain regions critical for the underlying behavioral phenotypes in which pyramidal are not the primary neuronal subtype. To this end, we focused our attention on medium spiny neurons (MSNs) of the nucleus accumbens (NAc), a region highly involved in social reward and motivation. We subjected pregnant rat dams to cyclic bouts of hypoxia (GIH, 10.5% oxygen) and normoxia (GNX, 21% oxygen) for eight hours during their resting period. The current experiment analyzed spine densities across the core and shell substructures of the NAc. Cortical slices of post-pubescent (P37-P43) Sprague-Dawley rat brains were stained via a gene gun delivery of DiI-fluoresced tungsten bullets to illuminate dendritic spines and quantify based on their morphology (stubby, thin, mushroom). Subjects included male (n = 10 GNX, 9 GIH) and female (n = 8 GNX, 9 GIH) offspring to compare sex differences in spine density alterations. In contrast to what we had found for cortical dendritic spines, we found no statistically significant differences of total spine densities or subtype densities across the core or shell of any experimental group, regardless of sex. This indicates that in the offspring there is differential susceptibility of glutamatergic cortical pyramidal neurons vs. ventral striatal medium spiny neurons to the effects of maternal GIH. Current efforts are aimed at identifying the biochemical mediators that contribute to these regional spine differences.

Disclosures: T.L. Ziehm: None. **D.R. Anderson:** None. **M.J. Andersen:** None. **J.J. Watters:** None. **T.L. Baker:** None. **M.E. Cahill:** None.

Poster

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.03/J6

Topic: B.05. Synaptic Plasticity

Support: IBS-R001-D3-2026

Title: Investigation of synaptic dynamics between CA1 and ACC during remote memory formation

Authors: *H. PARK[1,3], C. LEE[4], J. KIM[4], H. JUNG[1], Y. SUNG[5], B.-K. KAANG[2];
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Abstract: During systems consolidation, memory representations initially encoded in the hippocampus are progressively reorganized across distributed cortical regions, including the anterior cingulate cortex (ACC). Previous studies have largely investigated hippocampal-cortical interactions through neuronal coactivity and oscillatory synchronization. However, the direct synaptic connectivity and accompanying structural dynamics that support this process remain unclear. In this study, we aim to visualize direct synaptic connections and characterize the

synaptic dynamics between the hippocampus and cortex during systems consolidation. Using dual-eGRASP, we will monitor synaptic changes across multiple time points to elucidate the synaptic mechanisms underlying systems consolidation.

Disclosures: H. Park: None. **C. Lee:** None. **J. Kim:** None. **H. Jung:** None. **Y. Sung:** None. **B. Kaang:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.04/J7

Topic: B.05. Synaptic Plasticity

Support: IBS-R001-D3

Title: Investigation of presynaptic and postsynaptic structural plasticity underlying engram synapse network after learning

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Abstract: Neuronal activity induce structural plasticity, therefore governs future network activity. In The synaptic network among interregional engram neurons, which exhibit experience-dependent synaptic plasticity, is thought to underlie memory consolidation and retrieval after learning. However, how the pre-existing synaptic network and the neuronal activity during learning influence engram allocation and new engram synapse formation is poorly understood. By longitudinally tracking CA3-CA1 dendrites in vivo, we found that dendritic segments with higher pre-learning synaptic turnover were allocated to become engrams after learning. However, the addition of newly formed E-E synapses after learning occurred irrelevant to pre-learning turnover, suggesting that the structural plasticity is induced by neuronal activity during learning. Moreover, the axons from presynaptic engrams showed higher rates of the multisynaptic boutons two days after learning, further suggesting that structural changes of pre- and postsynaptic compartments collectively underlie newly formed engram synapses.

Disclosures: Y. Sung: None. **C. Lee:** None. **H. Jung:** None. **H. Park:** None. **B. Kaang:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.05/J8

Topic: B.05. Synaptic Plasticity

Support: NIHR01AA027231
NIHR01MH084894
T32DA007027

Title: Psilocybin affects insular cortex and ventral hippocampal perineuronal nets and conditioned taste aversion

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Abstract: In recent years, the psychedelic compound psilocybin has emerged as a promising therapeutic for a wide variety of psychiatric conditions, including major depressive disorder and substance use disorders. Psilocybin's therapeutic efficacy for each may be related to its ability to promote neuroplasticity in the brain, potentially through agonism of the serotonin 2A receptor (5-HT_{2A}R). Perineuronal nets (PNNs) are extracellular matrix structures that primarily surround parvalbumin (PV)-expressing interneurons and restrict neuroplasticity in the adult brain. To investigate whether psilocybin modulates PNNs, we used the plant lectin *Wisteria floribunda* agglutinin (WFA) to visualize PNNs and anti-PV antibodies to identify PV+ neurons in adult C57BL/6J or 5-HT_{2A}R knockout mice. Tissue was collected either 2.5 or 24 hours after intraperitoneal injection of 1 mg/kg psilocybin and both cortical and hippocampal regions were imaged and analyzed. Psilocybin did not affect PNNs or PV neurons in the anterior cingulate cortex or dorsal hippocampus at either time point. However, the intensity of PNNs was reduced in the insular cortex and ventral hippocampus of psilocybin-treated female mice after 2.5 hours, which can indicate a "reopening" of plasticity in these regions. Notably, these effects were absent 24 hours post-treatment and in 5-HT_{2A}R knockout mice, indicating the response is both transient and may be receptor-dependent. Next, we determined whether psilocybin would induce a conditioned taste aversion (CTA), a behavior regulated in part by the insula and ventral hippocampus. CTA utilizes classical conditioning to evaluate internal state of an animal as well as aversive memory retention and retrieval. Both 1 and 3 mg/kg, but not 0.3 mg/kg, psilocybin induced a CTA in males and females. We also analyzed PNNs and PV neuron number and intensity in the insula after acquisition and retrieval of CTA. Preliminary data indicates that PNN and PV intensity were decreased, implicating insula PV neurons and PNNs in CTA. These results warrant further investigation into the mechanisms behind psilocybin's modulation of PNNs and how they can be harnessed to alter behavior.

Disclosures: A.L. Zylko: None. **M. Saraswat:** None. **S. Todupunoori:** None. **L. Davies:** None. **C. McComb:** None. **J. Gonzalez-Maeso:** F. Consulting Fees (e.g., advisory boards); Boston Interactome. **A.W. Lasek:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Program #/Poster #: PSTR044.06/K1

Topic: B.05. Synaptic Plasticity

Support: UC Irvine Chancellor's Postdoctoral Fellowship
AP Giannini Postdoctoral Research Fellowship

Title: Spatial transcriptomics reveals modified transcript levels in cell bodies and dendrites of adult dentate granule cells growing in response to PTEN deletion

Authors: *J. M. YONAN[1], O. STEWARD[2];
[1]Univ. of California, Irvine, Irvine, CA; [2]Reeve-Irvine Res. Ctr., Univ. of California Irvine, Irvine, CA

Abstract: The mechanistic target of rapamycin (mTOR) pathway is a major regulator of cell growth and proliferation during development. Mutations in the upstream regulator of mTOR, phosphatase and tensin homolog (PTEN), have been implicated in human disorders, including epilepsy. We previously reported that focal, vector-mediated PTEN deletion in the adult dentate gyrus triggers growth of mature granule cells, increased network connectivity due to adult synaptogenesis, and eventual seizures. While the canonical view of mTOR activation would implicate increases in protein translation for the resulting neuronal growth, such drastic effects could also involve alterations in gene expression that are currently unknown. Here, we utilize spatial transcriptomics to assess gene expression profiles in dentate granule cell bodies and dendrites during growth. PTEN-floxed/Rosa-reporter mice received unilateral injections of AAV-Cre into the dentate gyrus. Our previous reports define 3 phases: 1) soma size increases from 0-2 months after PTEN deletion, 2) cell body and process growth from 2-4 months, and 3) a slower state of growth from 4-6 months. To sample transcriptional profiles during these time periods, brains were collected at 1-, 3-, and 5-months post injection. Differentially-expressed genes (DEGs) were identified by comparing gene expression profiles in PTEN deleted dentate granule cells vs. PTEN-expressing cells in the contralateral dentate gyrus. Initial assessment of transcriptional profiles within the granule cell layer revealed different assortments of DEGs over time. Unique transcriptional changes were also identified in the inner, middle and outer dendritic laminae, which are contacted by different input pathways (perforant path vs. commissural/associational inputs). In both cell body and dendritic layers, DEGs increased over time, even into the period when growth had slowed. Notably, despite expansion of the mossy fiber terminal field in CA3, there were minimal differences in transcripts in the lamina containing mossy fiber terminals and postsynaptic dendrites of CA3 neurons. Analyses of tissue from a control, Rosa-reporter mouse that received a comparable AAV-Cre injection displayed subtle increases in GFAP in dentate granule cells expressing tdT vs. the contralateral side, with no other transcriptional changes detected. The role of DEGs identified here during adult neuron growth induced by PTEN deletion remains to be defined.

Disclosures: J.M. Yonan: 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 seeking to develop novel therapies for neurological disorders.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.07/K2

Topic: B.05. Synaptic Plasticity

Support: Intramural Research Program, National Institute of Environmental Health Sciences, NIH grant Z01 ES100221 (SMD)

Title: Cell-Type Specific Roles of Perineuronal Nets in Hippocampal Excitability and Seizure Severity

Authors: *G. M. ALEXANDER[1], S. M. DUDEK[2];
[1]Natl. Inst. of Envrn. Hlth. Sci., Durham, NC; [2]Neurobio. Lab., NIH, Research Triangle Park, NC

Abstract: Perineuronal nets (PNNs) are specialized extracellular matrices composed of chondroitin sulfate proteoglycans (CSPGs) that encase select neuronal populations. These include parvalbumin (PV)-expressing interneurons throughout the brain and hippocampal CA2 pyramidal neurons, which lack typical long-term potentiation (LTP) in the stratum radiatum. We previously demonstrated that PNN digestion enables LTP in CA2 neurons, suggesting that PNNs can ultimately regulate CA2 neuronal activity. Conversely, we found that staining for CA2 PNNs is activity-regulated: chronic chemogenetic excitation decreases PNNs, whereas inhibition increases them. As work by Scharfman and colleagues has shown that CA2 is a key node in regulating seizure activity, determining the role of CA2 PNNs in relation to seizures is of critical importance.

We next sought to determine whether PNNs change following kainic acid (KA)-induced status epilepticus (SE), and whether this affects CA2 and PV cells similarly. Wild-type mice received repeated injections of a low-dose of KA (5 mg/kg every 30 min) to induce SE. PNNs measured using WFA staining was quantified 7 days later and compared with saline-injected animals. We found that CA2 pyramidal cell PNNs decreased in KA-treated animals compared to controls, whereas PV cell WFA staining remained unchanged.

Next, we examined how genetic deletion of PNNs from specific cell types alters responses to KA. Using floxed aggrecan (Acan fl/fl) mice crossed with either Amigo2-Cre (CA2-targeted) or PV-Cre mice, we selectively depleted PNNs from either CA2 or PV cells, respectively. Using cFOS staining as an estimate of neuronal activity, we found that a single injection of (sub-seizure) KA yielded greater staining in animals lacking CA2 PNNs compared to Cre- control mice. Repeated KA administration to induce SE increased mortality in mice lacking CA2 PNNs, though the number of injections required to reach SE did not differ from Cre- control animals. Additionally, local field potential recordings during KA treatment revealed a greater cumulative duration of electrographic seizure activity in mice lacking CA2 PNNs. In contrast, cFOS staining so far show no differences in after a single KA injection in PV-Cre+; Acan fl/fl mice compared to KA injection in control PV-Cre- tissue, but they required more injections to reach SE than

Cre- controls. These findings suggest that PNNs on CA2 neurons restrict excitatory activity, while those on PV cells promote it, likely by driving network synchronization and gamma oscillations. Thus, the findings from our work point toward divergent roles of PNNs in seizure susceptibility and associated network changes.

Disclosures: G.M. Alexander: None. **S.M. Dudek:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.08/K3

Topic: B.05. Synaptic Plasticity

Title: Development of a glutamatergic-like cell line to investigate synaptic changes occurring in autism spectrum disorder

Authors: *A. K. BHATTI[1], S. NANDI[2], B. GETACHEW[1], R. L. COPELAND, Jr.[1], Y. TIZABI[1];
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Abstract: Background: Autism spectrum disorder (ASD) is a serious neurodevelopmental disorder that significantly affects the quality of life. The cause and treatment remain elusive, although alterations in the formation of excitatory (glutamatergic) and inhibitory (GABAergic) synapses, as well as imbalances in excitatory-inhibitory synaptic transmission and exposure to some drugs (such as valproate) have been implicated. Thus, further elucidation of these synaptic abnormalities might provide novel targets in prevention and/or treatment of this devastating disorder. The aim of this study is to provide a robust cellular model, particularly a glutamatergic type, to evaluate some of these parameters.
Methods: We used SHSY-5Y cells, an immortalized cell line derived from human neuroblastoma, to differentiate them into glutamatergic-like neurons. We applied a relatively high concentration of B27 (5%), a serum-free, nutrient-rich supplement widely used for this purpose, for 12 days. Neurite outgrowth and synaptic markers specific to neurons in general, and glutamatergic ones, in particular were evaluated by Brightfield microscopy, and Western blot, respectively.
Results: Morphological observations included substantial lengthening of neurites suggesting neuronal characteristics. Moreover, there was a significant increase in expression of postsynaptic density protein-95 (PSD-95), a highly specific postsynaptic glutamatergic protein.
Conclusion: This technique provides a simple but reliable method to generate glutamatergic-like neuronal cells as a valuable tool in drug development and discovery. Specifically, it can be used to investigate synaptic changes in ASD and to identify novel targets.

Disclosures: A.K. Bhatti: None. **S. Nandi:** None. **B. Getachew:** None. **R.L. Copeland:** None. **Y. Tizabi:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Program #/Poster #: PSTR044.09/K4

Topic: B.05. Synaptic Plasticity

Support: T32 HD007491

Title: Neuronal Activity-Dependent Extracellular Matrix Remodeling

Authors: *A. LARSEN, S. PARK;
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Abstract: Emerging evidence implicates the extracellular matrix (ECM) as a regulator of memory. Neural activity has been shown to remodel the ECM through activation of ECM-degrading enzymes and induction of individual ECM components, suggesting a potential mechanism for its role in memory processes. However, the localization of ECM clustering within synaptic architecture and how neuronal activity reshapes these structures remains poorly understood. Addressing these questions requires ultrastructural analyses of synaptic ECM. However, because brain ECM lacks intrinsic electron density, direct visualization of ECM at synapses by electron microscopy (EM) remains challenging. To overcome this limitation, we developed ECM labeling probes based on Hapln1, an ECM link protein essential for proper matrix assembly. The first tool, HRP-Link, fuses Horseradish peroxidase to Hapln1 to generate electron-dense ECM labeling detectable by EM. Mice received hippocampal HRP-Link injections on P2, and tissue was analyzed at 6 weeks by DAB staining and transmission EM. We observed lattice-like ECM clusters surrounding excitatory synapses. Notably, these clusters were positioned between astrocytic processes and the synaptic cleft, as well as surrounding the tripartite synapse. To investigate activity-dependent remodeling, we used ex vivo stimulation paradigms and H-Link, a HaloTag-Hapln1 fusion probe, to monitor ECM dynamics. Administration of HaloTag ligands (HTLs) enables assessment of remodeling dynamics. Mice received hippocampal H-Link injections on P2. At 6-8 weeks, acute hippocampal slices were incubated in HTL549 to label pre-existing H-Link clusters. Slices were stimulated with a 3-minute KCl pulse, then allowed to recover for four hours. As a control, adjacent slices were treated with an equimolar NaCl solution. Interestingly, KCl induced a robust reduction of pre-existing H-Link in dendritic layers compared to controls (n=4). To test whether a physiologically relevant stimulus produced similar effects, we used theta-burst stimulation (TBS) to induce long-term potentiation in CA1 stratum radiatum dendrites. TBS reduced H-Link labeling in the stimulated dendritic region within two hours (n=1). These findings establish an ex vivo pipeline for studying spatiotemporal dynamics of ECM remodeling. By defining the spatial organization of ECM clusters within hippocampal synaptic architecture and identifying and early activity-dependent ECM degradation response, this work provides critical framework for investigating the role of ECM dynamics in memory-related processes.

Disclosures: A. Larsen: None. **S. Park:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Program #/Poster #: PSTR044.10/K5

Topic: B.05. Synaptic Plasticity

Title: Psychedelic Psilocybin and DOI's Effect on Nucleus Accumbens Core Structural and Functional Synaptic Plasticity.

Authors: *K. M. RHYNER[1], J. NATARAJAN[1], J. P. TABORDA-BEJARANO[2], J. MCCORVY[3], J. HENNESSEY[1], J. J. TUSCHER[1], M. C. HEARING[4], C. GARCIA-KELLER[1]; [1]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI; [2]Pharmacol. and Toxicology, Med. Col. of Wisconsin, Wauwatosa, WI; [3]Cell Biology, Neurobio. and Anat., Med. Col. of Wisconsin, Medical College of Wisconsin, WI; [4]Dept. of Biomed. Sci., Marquette Univ., MILWAUKEE, WI

Abstract: Psychedelics produce rapid and sustained therapeutic effects that are thought to arise from their ability to promote neuroplasticity through serotonin 2A (5-HT2A) receptor signaling. However, the effects of psychedelics on structural and functional plasticity within the nucleus accumbens core (NAcore), a brain region critical for reward, motivation, and neuropsychiatric disorders, remain poorly understood. We investigated whether the 5-HT2-family receptor agonist DOI and the clinically relevant psychedelic, psilocybin (PSI), alter medium spiny neuron (MSN) morphology and excitatory synaptic transmission in the rat NAcore. Open-field behavioral testing revealed significant increases in wet-dog shakes, a well-established behavioral marker of serotonergic activity, following DOI and PSI administration. Notably, female rats exhibited greater DOI-induced wet-dog shake behavior than males, indicating sex-dependent behavioral responses. Confocal imaging, three-dimensional reconstruction, and analysis of lipophilically labeled MSNs demonstrated significant increases in dendritic spine density in female rats 24 h after DOI or PSI treatment, whereas males showed minimal structural changes. DOI-induced increases in spine density persisted for at least 3 weeks following treatment. Pretreatment with the selective 5-HT2A receptor antagonist MDL100,907 prevented both DOI-induced wet-dog shakes and dendritic spine remodeling, supporting a critical role for 5-HT2A receptor signaling in the NAcore. Then, to determine whether structural changes were accompanied by functional adaptations, whole-cell patch-clamp recordings were performed in NAcore MSNs. DOI treatment significantly increased spontaneous excitatory postsynaptic current (sEPSC) amplitude and increased sEPSC frequency 24 h after treatment in female rats, consistent with enhanced excitatory synaptic strength. Together, these findings demonstrate that a single psychedelic exposure induces robust and long-lasting structural and functional synaptic plasticity within the NAcore in a sex-dependent manner. These results identify the NAcore as a previously underappreciated target of psychedelic action and suggest that enhanced plasticity in females may contribute to differential sensitivity to psychedelic-induced neural remodeling.

Disclosures: K.M. Rhyner: None. **J. Natarajan:** None. **J.P. Taborda-Bejarano:** None. **J. McCorvy:** None. **J. Hennessey:** None. **J.J. Tuscher:** None. **M.C. Hearing:** None. **C. Garcia-Keller:** None.

Poster

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Program #/Poster #: PSTR044.11/K6

Topic: B.05. Synaptic Plasticity

Support: RS-2025-25459402
RS-2025-16070516

Title: Activity-dependent Neuroligin-1 cleavage in peri-infarct cortex may promote synaptic remodeling after ischemic stroke

Authors: *J. YOON[1], B. G. KIM[2,4], H. KIM[3,4];
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Abstract: Ischemic stroke disrupts synaptic connectivity and neural circuit function. Synaptic plasticity and remodeling occur as part of spontaneous recovery in the peri-infarct cortex and other regions. Synaptic adhesion molecules mediate pre- and postsynaptic contacts and regulate synapse formation, maintenance, and function; however, their regulation during post-stroke reorganization remains unclear. Neuroligin-1 (NLGN1), a key postsynaptic adhesion molecule interacting with presynaptic neurexins, undergoes activity-dependent proteolytic cleavage. We hypothesized that stroke-induced NLGN1 cleavage transiently weakens synaptic adhesion, creating a permissive state for synaptic remodeling during recovery. Focal ischemic injury was induced via photothrombotic stroke in 8-week-old mice male and female mice (n=4/group). Peri-infarct cortical tissue was collected for biochemical fractionation and Western blot analysis. Membrane and soluble fractions were separated by ultracentrifugation. Stroke mice showed decreased full-length NLGN1 and increased soluble NLGN1 fragments compared to sham, suggesting enhanced ectodomain shedding after stroke. To assess whether NLGN1 cleavage weakens synaptic adhesion, synaptosome fractions were isolated at day 7 post-stroke. Presynaptic VGLUT2 levels were similar between groups, but postsynaptic PSD-95 was significantly reduced in stroke animals. The decreased PSD-95/VGLUT2 ratio indicates relative loss of postsynaptic components, suggesting weakened synaptic adhesion after stroke. We then examined activity-dependent NLGN1 cleavage *in vitro*. Primary cortical neurons from TP18 SD rats (n=5) were treated with bicuculline or tetrodotoxin for 24 hours. Full-length NLGN1 decreased in lysates and soluble NLGN1 increased in conditioned medium under both conditions. Unchanged NLGN1 mRNA levels confirmed proteolytic cleavage rather than transcriptional regulation. The responsible enzyme will be identified using this model. Our

findings demonstrate that activity-linked NLGN1 cleavage is induced after ischemic stroke, potentially weakening synaptic adhesion and promoting remodeling in the peri-infarct cortex. This mechanism may represent a recovery-associated pathway linking altered neuronal activity to synaptic reorganization after stroke.

Disclosures: J. Yoon: None. **B.G. Kim:** None. **H. Kim:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Program #/Poster #: PSTR044.12/K7

Topic: B.05. Synaptic Plasticity

Support: JST-CREST 2622JrB27c

Title: Microglial contribution for multisensory associative learning in higher visual cortex

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Abstract: Multisensory integration is essential for recognizing external objects and environments, and sensory associative learning, which links specific sensory cues to behavioral outcomes, is critical for survival. Although previous studies have shown that the mouse posterior parietal cortex (PPC) contributes to sensory integration and is modulated by learning, the neuronal and synaptic mechanisms by which sensory information is integrated during learning remain unclear. Here, we focused on the anterolateral visual area (AL), a subregion of the mouse PPC. Using *in vivo* calcium imaging, we visualized population responses in AL to whisker stimulation (W), auditory stimulation (A), and combined whisker-auditory stimulation (WA). Distinct but partially overlapping neuronal populations responded to W, A, and WA. We then trained mice in a whisker-auditory discrimination task in which reward was delivered only after the combined WA stimulus, but not after either unimodal stimulus. During learning, sensory-responsive populations were reorganized: the proportion of WA-responsive neurons, representing reward-associated stimuli, increased, whereas neurons responding to non-reward-associated stimuli did not significantly change. Pharmacological ablation of microglia with CSF1R inhibitor PLX3397 impaired discrimination learning and prevented this learning-associated reorganization. To elucidate local circuit mechanisms driving these changes, we used two-photon holographic optogenetics to stimulate individual sensory-responsive neurons while monitoring surrounding network activity. WA-responsive neurons showed increased functional connectivity after learning, suggesting strengthening of local circuits among reward-associated neurons. To investigate whether these neuronal activity changes were underpinned by synaptic plasticity, *in vivo* imaging with the glutamate sensor iGluSnFR was performed. Spines belonging

to non-reward-associated clusters were preferentially eliminated, whereas spines newly formed during learning were preferentially incorporated into reward-associated WA clusters. These spine dynamics were absent in microglia-ablated mice, suggesting that microglia remodel synapses in a manner dependent on local dendritic activity during sensory associative learning. Together, our findings reveal a microglia-dependent mechanism by which local neuronal circuits in AL are reorganized to support learned multisensory integration, providing insight into sensory dominance and psychiatric disorders characterized by abnormal sensory integration.

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Poster

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Program #/Poster #: PSTR044.14/L1

Topic: B.05. Synaptic Plasticity

Support: Moore Foundation

Title: Capturing drug-induced proteomic changes in active neurons with a split-TurboID

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Abstract: Understanding how plasticity-modulating drugs can alter neuronal circuitry at the molecular level requires tools that capture activity-dependent proteomes in awake, behaving mice. CaST (Ca^{2+} Split TurboID) is a proximity-labeling approach in which split-TurboID reconstitutes in a calcium-dependent manner, enabling biotinylation of proteins preferentially in active neurons. We leveraged CaST, delivered via AAV-PHP.eB intracerebroventricular injection (AAVPHP.eB-Syn-CD4-sTC-M13-GFP + AAVPHP.eB-Syn-CaM-V5-sTN) in neonatal pups, to assess whether we can perform activity-dependent protein enrichment following a drug or saline administration in mice (n=2 per group).; 20 mg/kg) and biotin (24 mg/kg) to mice, and sacrificed animals 90 minutes later. The frontal cortex was microdissected and homogenized, and biotinylated proteins were enriched by streptavidin pulldown and identified by mass spectrometry using DIA-PASEF approach. Data were analyzed using Spectronaut 20.Differential analysis of our pilot dataset identified candidate proteins significantly altered in 5-MeO-DMT-treated mice compared to saline-treated mice. Upregulated candidates ($log2fc \geq 0.58$, $q < 0.05$) in this preliminary study include Cdh2 (N-cadherin), a mediator of synaptic adhesion and structural remodeling, and Dynlrb1, a dynein light chain involved in cytoskeletal motor transport. Downregulated candidates ($log2fc \leq -0.58$, $q < 0.05$) include Lamb2, which encodes a laminin subunit implicated in extracellular matrix organization. Together, these hits point towards programs of cytoskeletal reorganization, synaptic remodeling, and growth signaling consistent with structural plasticity.These results provide proof of principle

that CaST can be used to perform activity-dependent protein labeling in vivo in the mouse brain and demonstrate the utility of CaST for enabling brain-state-dependent proteomics.

Disclosures: C. Leung: None. **K. Giri:** None. **D. Kim:** None. **K. Adams:** None. **M. Anguiano:** None. **C.K. Kim:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.15/L2

Topic: B.05. Synaptic Plasticity

Support: DP2MH136588
SSP-2022-107
1019469

Title: Synaptosome resolved proteomics and HaloTag pulse-chase imaging reveal molecular and structural remodeling of mPFC excitatory synapses following 5-MeO-DMT exposure

Authors: *K. GIRI[1], D. KIM[1], K. ADAMS[1], J. MUIR[1], C. LEUNG[1], B. PHINNEY[2], C. K. KIM[1];
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Abstract: Psychoplastogens such as 5-MeO-DMT drive rapid synaptic remodeling, yet the compartment-specific molecular mechanisms underlying these effects in the medial prefrontal cortex (mPFC), a region central to cognition and mood, remain unresolved. Male C57BL/6J mice (6-8 weeks; n=4/group) received a single intraperitoneal injection of 5-MeO-DMT or saline and were sacrificed 90 minutes later. Bilateral mPFC was microdissected and synaptosomes isolated by sucrose-gradient ultracentrifugation. Synaptosomal morphology was confirmed by electron microscopy. Samples were trypsin digested and peptides separated on an Evosep system coupled to a Bruker timsTOF mass spectrometer operating in DIA-PASEF mode. Data were processed using Spectronaut for protein identification and quantification. To track surface AMPAR dynamics, cultured rat cortical neurons expressing HaloTag-GluA1 (HT-GluA1) were subjected to pulse-chase labeling with membrane-impermeable HaloTag ligands following 5-MeO-DMT or saline treatment. EPSILON imaging was performed in vivo to confirm new dendritic spine formation. Approximately 2,200 protein groups were quantified across experimental conditions with 1% FDR confidence. PCA showed clear separation between saline and 5-MeO-DMT treated samples, indicating distinct synaptic proteomic profiles. SynGO analysis revealed that 51.4% of quantified proteins were annotated as synaptic, supporting the specificity of the synaptosome preparation. Proteins altered by 5-MeO-DMT were enriched in pathways associated with membrane trafficking, synaptic signaling, cytoskeletal remodeling, and translational regulation. Notably, sorting nexin-27 (SNX27), ELAV-like RNA-binding proteins, and cartilage acidic protein-1 (CRTAC1) were upregulated following 5-MeO-DMT treatment,

suggesting enhanced receptor recycling and activity dependent translational control during psychoplastogen induced plasticity. Complementary HaloTag pulse-chase imaging demonstrated increased surface GluA1 insertion and enhanced dendritic spine formation following 5-MeO-DMT relative to saline control (p=0.012), in vitro as well as in vivo conditions. In summary, synaptosome proteomics combined with HaloTag imaging revealed compartment-specific protein alterations and new dendritic spine formation following 5-MeO-DMT, linking synaptic molecular remodeling to structural plasticity relevant to neuropsychiatric disease.

Disclosures: K. Giri: None. **D. Kim:** None. **K. Adams:** None. **J. Muir:** None. **C. Leung:** None. **B. Phinney:** None. **C.K. Kim:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.16/L3

Topic: B.05. Synaptic Plasticity

Support: NSF REU Grant

Title: Investigating the Role of GPM6A in Synaptic Pruning and Schizophrenia Development

Authors: *A. BROWN-OGHA;
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Abstract: Schizophrenia is a severe neuropsychiatric disorder affecting over 24 million people worldwide. Altered glutamatergic synapse development and excessive synaptic pruning have been implicated in schizophrenia pathogenesis, potentially contributing to excitatory/inhibitory imbalance and downstream dopamine dysregulation. However, current medications, primarily antipsychotics, target dopamine dysregulation and remain ineffective for approximately 30% of diagnosed patients experiencing treatment resistance. Further study of schizophrenia-associated genes regulating synaptic pruning is critical to improving our understanding and treatment of this disorder. *GPM6A*, a schizophrenia-associated gene, encodes M6a, a neuronal membrane glycoprotein localized to the presynaptic membrane, active zones, and potentially the postsynaptic membrane. M6a is involved in neuronal development, synaptogenesis, and synaptic plasticity, but its role in schizophrenia pathogenesis remains poorly defined.To investigate this, we studied the *Drosophila* ortholog of *GPM6A*, *M6*, and induced neuron-specific knockdown using the elav-Gal4/UAS-RNAi system. Glutamatergic synapses at the larval neuromuscular junction between muscles 6 and 7 in segment A2, a well-characterized model system, were visualized using antibody staining and confocal microscopy. To evaluate behavioral phenotypes relevant to schizophrenia, we performed social-space and olfactory-memory assays. *M6* knockdown resulted in ghost boutons lacking active zones and a reduced average number of active zones per bouton, suggesting the accumulation and impaired clearance of nonfunctional synapses. Additionally, we observed disrupted colocalization of certain boutons with glutamate

receptors, suggesting a distinct ghost bouton subclass. Behaviorally, while social spacing appeared unaffected, *M6* knockdown flies exhibited impaired odor-preference learning.These findings implicate *GPM6A* in synapse formation and clearance, processes relevant to schizophrenia pathogenesis. By linking structural synaptic changes with learning deficits, this study highlights *M6/GPM6A* as a potential contributor to altered glutamatergic synapse regulation in schizophrenia and supports further investigation into presynaptic membrane proteins as candidate targets for therapeutic intervention beyond the dopamine axis.

Disclosures: A. Brown-Ogha: None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.17/L4

Topic: B.05. Synaptic Plasticity

Support: NSF GRFP
Gruber Graduate Science Fellowship

Title: C. elegans as a model to uncover the cellular mechanisms of psychedelic drugs

Authors: *R. VACA;
Interdepartmental Neurosci. Program, Yale, New Haven, CT

Abstract: Psychedelics are emerging as promising therapeutics for depression, anxiety, PTSD, and addiction, yet the mechanisms underlying their lasting clinical benefits remain poorly understood. A prevailing model holds that psychedelics act through serotonin signaling to promote dendritic spine growth and synaptic plasticity. However, these compounds likely engage multiple molecular targets, and the relative contribution of each to therapeutic outcomes is unclear. Whether psychedelic-induced structures integrate into functional circuits also remains unknown. Dissecting these questions requires a system that enables causal genetic tests, functional readouts, and unbiased screening—capabilities that are limited in mammalian models. We have established Caenorhabditis elegans as a genetically tractable platform for studying conserved mechanisms of psychedelic action. Using DOI (2,5-dimethoxy-4-iodoamphetamine), a well-characterized 5-HT2A agonist and hallucinogen, we find that DOI induces robust, persistent dendritic spine growth in C. elegans neurons. Strikingly, DOI also suppresses axon degeneration caused by energetic stress, revealing a previously undescribed neuroprotective phenotype with potential relevance to neurodegeneration, injury, and repair. Neither spine growth nor neuroprotection is recapitulated by serotonin treatment, indicating that DOI can act through serotonin-independent mechanisms and motivating an unbiased search for conserved effectors. To identify these effectors, we have begun forward genetic screens for mutants in which DOI fails to promote spine growth. These screens have already recovered candidate mutants, demonstrating the feasibility of unbiased genetic dissection of psychedelic action in this system.

In parallel, we are leveraging the stereotyped wiring, defined synaptic partners, and single-cell genetic tools of C. elegans to determine whether DOI-generated spines and rescued axons form appropriate functional connections—a question that has been technically intractable in mammalian systems. Together, these findings position C. elegans as a powerful new model for psychedelic neuroscience: the conservation of spine growth in an invertebrate nervous system points to fundamental structural-plasticity mechanisms, the dissociation between DOI and serotonin challenges serotonin-centric models, and the discovery of psychedelic-induced neuroprotection broadens the potential clinical scope of these compounds beyond psychiatry.

Disclosures: R. Vaca: None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.18/L5

Topic: B.05. Synaptic Plasticity

Support: AARG-NTF-23-1150820 (Alzheimer's Association)
NIH R01AG091548

Title: Aβ reshapes synaptic nano-Architecture to drive spine-specific vulnerability and compensation via ephrin-B3 signaling

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Abstract: The loss of excitatory synapses that form on dendritic spines underlies cognitive decline in Alzheimer's disease (AD). By binding to spines, pathological hallmarks of AD - Aβ and Tau - perturb synaptic function and plasticity, yet how diverse synapses succumb to AD pathology remains unknown. In this study we utilized Stimulated Emission Depletion (STED) nanoscopy in fixed and living cultured cortical neurons to monitor how Aβ disrupts nano-organization of endogenous proteins in spines synapses. Prior work demonstrated that aligned nanomodules of pre-synaptic and post-synaptic proteins (e.g., Bassoon, SYT1, VGluT1, PSD-95) form building blocks of dendritic spine synapses, and the formation of new aligned nanocluster units underlies spine structural plasticity. Aβ disrupted this nano-organization in unexpected ways. Rather than leading to uniform loss of nanomodules in all spines in an LTD-like manner, Aβ selectively **destabilized PSD-95 in the smallest spines,** which typically contain only one nanomodule. In contrast, **larger spines with multiple PSD-95 nanomodules were structurally preserved,** and some even increased in size—suggesting a **compensatory response** at these more stable synapses. Mechanistically, we found that Aβ induces robust phosphorylation of S332 within the intracellular domain of trans-synaptic organizer ephrin-B3, which was previously shown to disrupt PSD-95 localization and stabilization in dendritic spines. Strikingly, molecular replacement experiments of endogenous ephrin-B3 with a non-phosphorylable

(S332A) ephrin-B3 mutant rescued the Aβ-dependent disassembly of spines with simple nano-architecture. These findings show that spines with different nano-architectures respond differently to Aβ likely through modifying the signaling of trans-synaptic organizing molecules that are critical for excitatory synapse formation and plasticity. Our imaging provides unique nanoscale insight into how Aβ may shift the balance between LTP and LTD in AD. Understanding this interplay of synaptic vulnerability and local compensation could open new avenues for restoring synaptic function in Alzheimer's disease.

Disclosures: A. Skeens: None. **J. Scripter:** None. **Y. Akter:** None. **M. Hruska:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR044.19/L6

Topic: B.05. Synaptic Plasticity

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Title: The Role of NCAM2 in adult synaptic plasticity

Authors: *A. PARCERISAS[1,4], A. ORTEGA[2,6], L. GUZMAN[7], E. ROJO-FRANCÀS[8], F. MIGUEZ CABELLO[3], D. SOTO[3,6], X. GASULL[3,6], M. BOSCH[8], Y. MANSO[1,9], E. SORIANO[1,9], L. PUJADAS[5,10,1,9];
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Abstract: Adult neuronal plasticity, the nervous system's remarkable ability to adapt and reorganize in response to experiences, remains a central focus in neuroscience. Synaptic plasticity is considered the primary mechanism driving this adaptability and is crucial for

learning, memory, and cognitive functions throughout life. At the molecular level, extracellular matrix molecules, such as Reelin, and transmembrane cell adhesion molecules (CAMs) play an important role in regulating and adapting synaptic changes, with important implications in pathology. CAMs have emerged as key elements in the regulation of adult neuronal plasticity, playing prominent roles in controlling synapse formation and maintenance. Neural Cell Adhesion Molecule 2 (NCAM2) is a cell adhesion molecule specifically expressed in brain that wefound crucial for proper neuronal morphogenesis and cortex formation. In our studies, we characterized the interactome of NCAM2, identifying over 100 proteins that interact with NCAM2. Furthermore, our proteomic data, analyzed using bioinformatic tools, revealed significant enrichments in gene ontology terms and cellular pathways linked to the cytoskeleton and important neural cognitive functions, such as synapse formation and synapse maintenance. Here we show that in the adult brain, NCAM2 plays a crucial role in proper synaptic plasticity. Our results indicate that NCAM2 is involved in synapse formation and stability, and that physiological levels of NCAM2 are essential for synapse maintenance in the adult nervous system. Moreover depletion of NCAM2 leads to dendritic spine constriction and a reduction in spine density. Conversely, elevated levels of the gene may enhance contact stabilization by increasing dendritic spine size. Adhesion molecules and components of the extracelular environment has been linked to neuroprotective and neurodegenerative mechanisms in pathology, including Alzheimer's disease. Therefore, the findings from this study on NCAM2 deepens our understanding of the synaptic deficits associated with these conditions and pave the way for promising new research directions.

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Poster

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Program #/Poster #: PSTR044.20/L7

Topic: B.05. Synaptic Plasticity

Support: JSPS KAKENHI Grant JP26K02129

Title: Vesicular GABA transporter expression levels shape presynaptic ultrastructure at medium spiny neuron-pallidal terminals

Authors: *Y. SAITO[1], Y. ABE[1], Y. HIRAOKA[2], Y. YAMAZAKI[3], K. F. TANAKA[4];
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Abstract: The striatum is a central hub of basal ganglia circuits, and its output is dominated by GABAergic neurons called medium spiny neurons (MSNs). Although vesicular GABA transporter (VGAT) has traditionally been regarded as a protein which packages inhibitory neurotransmitters into synaptic vesicles, our previous findings suggest that VGAT may also contribute to structural changes of MSN-pallidal synapses. We previously reported that MSN-pallidal terminals become enlarged in disease-related and drug-induced brain states, such as L-DOPA-induced dyskinesia and tardive dyskinesia, and that this hypertrophy is associated with increased MSN VGAT expression. Similar presynaptic changes were also observed after antidepressant administration, suggesting that MSN terminals are structurally plastic across diverse brain states. However, how VGAT expression levels affect the ultrastructural components of inhibitory presynaptic terminals in vivo remains unclear.To examine VGAT-dependent presynaptic structural plasticity in vivo, we established a reliable, stable, and repeatable system for manipulating VGAT expression across pan-MSNs. We employed a tetO-based knock-in strategy for gain- and loss-of-function studies; we generated *Pde10a2*-tTA::VGAT$^{tetO/+}$ heterozygous mice for overexpression and *Camk2-tTS*::VGAT$^{tetO/tetO}$ homozygous mice for VGAT knockdown in MSNs. We confirmed corresponding changes in VGAT mRNA and protein expression using in situ hybridization and immunohistochemistry, respectively. We then examined the ultrastructure of inhibitory presynaptic terminals by transmission electron microscopy. Synaptic vesicle size, vesicle number, vesicle density, and terminal size were quantified in 50-nm ultrathin sections at either 15,000× or 60,000× magnification. We found that MSN VGAT overexpression enlarged presynaptic terminals, accompanied by a marked increase in synaptic vesicle number and an increase in individual vesicle size. In contrast, MSN VGAT knockdown did not markedly alter terminal size, but significantly reduced synaptic vesicle number, and density.Together, our findings demonstrated that the manipulation of VGAT expression levels directly affects inhibitory presynaptic ultrastructure in vivo. This work provides a previously underappreciated role of VGAT in presynaptic structural organization and supports the idea that synaptic vesicle protein levels can contribute to the ultrastructural architecture of inhibitory presynaptic terminals.

Disclosures: Y. Saito: None. **Y. Abe:** None. **Y. Hiraoka:** None. **Y. Yamazaki:** None. **K.F. Tanaka:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Topic: B.05. Synaptic Plasticity

Support: Murdock Foundation Partners in Science Award
NSF MRI 2117294

Title: Monocular Deprivation Reveals Activity-Dependent Control of Synaptic Spinules in Mouse V1

Authors: T. STAEHLE, *M. NAHMANI;
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Abstract: Synaptic spinules are finger-like projections from one neuron that embed themselves within the synaptic compartment of another neuron, most commonly the presynaptic bouton. These structures are evolutionarily conserved from invertebrates through humans, are present in up to 75% of excitatory presynaptic boutons, and spinule-bearing boutons (SBBs) form larger and stronger synapses than those without spinules. Further, synaptic spinules occur in at least two morphologically distinct forms, small clathrin-coated invaginations and larger uncoated projections, hinting at novel roles in neuronal communication and circuit stability. Yet despite their remarkable ubiquity, no published data address the function of synaptic spinules *in vivo*. To begin filling this gap, we examined whether manipulating neuronal activity alters the prevalence or morphology of spinules within SBBs. We used brain sections from male and female postnatal day 29 wild-type mice subjected to three days of monocular deprivation, a manipulation that allows direct comparison of activity-deprived and non-deprived circuits in primary visual cortex (V1). Transmission electron micrographs were analyzed for SBB prevalence and spinule morphology within monocular V1. We reasoned that if synaptic spinules serve as substrates for neuronal plasticity, SBB prevalence should decrease following activity deprivation during this critical period for visual plasticity in V1. Conversely, if spinules primarily stabilize synaptic function, large presynaptic boutons with the strongest synapses would be expected to retain their spinules. We found that brief activity deprivation altered both the prevalence and morphology of spinules within SBBs in deprived versus non-deprived hemispheres, suggesting synaptic spinules serve distinct functional roles within neocortical microcircuits.

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Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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Topic: B.05. Synaptic Plasticity

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NIH-NIMH Grant R03MH12740
NIH-NIDCD Grant R01DC019380

Title: Ionic direct current modulation of somatosensory circuit gain in Shank3-/- mice

Authors: *X. DENG, J. J. KIM, R. WANG, G. FRIDMAN, T. DEEMYAD;
Dept. of Otolaryngology-Head and Neck Surgery, Johns Hopkins Univ., Baltimore, MD

Abstract: Tactile hypersensitivity is a common sensory phenotype in autism spectrum disorder and is thought to reflect altered excitatory/inhibitory balance in sensory cortex. However, how local inhibitory circuit dysfunction changes cortical gain during tactile behavior remains unclear.

Shank3-/- mice provide a useful model because they show lateralized tactile hypersensitivity: the dominant paw is more sensitive to mechanical stimulation, and this behavioral asymmetry is associated with reduced PV+ basket cell density in layer 2/3 of the corresponding somatosensory cortex.
Here, we are developing an experimental framework to modulate and monitor somatosensory cortical gain in awake Shank3-/- mice. Forelimb dominance is first identified using a food-reaching task, allowing the dominant paw and corresponding S1 hemisphere to be defined for each animal. We then combine dual color in vivo two photon calcium imaging, automated von Frey stimulation, and ionic direct current (iDC) delivery through a microcatheter positioned under the cranial window. PV basket cells are targeted using an E2 enhancer driven red shifted calcium indicator, while pyramidal neurons are labeled with CaMKII-GCaMP6f. This approach allows simultaneous monitoring of inhibitory and excitatory components of L2/3 S1 during tactile stimulation and cortical gain modulation.Our findings show that tactile stimulation evokes stronger L2/3 pyramidal responses in the dominant hemisphere of Shank3-/- mice, consistent with increased gain in the circuit linked to the hypersensitive paw. In separate recordings, low amplitude iDC modulates calcium event amplitude without substantially changing event frequency, suggesting that iDC can adjust population gain without simply driving or silencing activity. Higher iDC amplitudes shift the network toward strong activation or suppression, defining a range in which gain modulation can be separated from direct excitation or inhibition.Using this approach, we will determine whether reducing gain in the dominant S1 hemisphere decreases pyramidal cell responses, restores PV basket cells /pyramidal balance, reduces response lateralization, and normalizes tactile hypersensitivity. Together, this work introduces a novel strategy for modulating sensory cortical gain during behavior and testing how local excitability contributes to tactile hypersensitivity in Shank3-/- mice.

Disclosures: X. Deng: None. **J.J. Kim:** None. **R. Wang:** None. **G. Fridman:** None. **T. Deemyad:** None.

Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Topic: B.05. Synaptic Plasticity

Support: NIH-NINDS Grant R01NS146406
NIH-NIMH Grant R03MH12740
NIH-NIDCD Grant R01DC019380

Title: Developmental astrocytic SHANK3 organizes perisynaptic astrocyte architecture for reliable sensory coding

Authors: *J. J. KIM, Y. CHEN, S. DILLON, N. HARDING, Y. SHU, S. G. SADEGHI, T. DEEMYAD;
Dept. of Otolaryngology-Head and Neck Surgery, Johns Hopkins Univ., Baltimore, MD

Abstract: Stable sensory processing requires more than maturation of neuronal synapses; it also depends on glial mechanisms that constrain excitation and preserve response timing across repeated stimuli. Astrocytes provide this control through fine perisynaptic processes and neurotransmitter transporters, but whether a developmental astrocyte program sets adult sensory circuit reliability is unknown.
Here we tested whether developmental astrocytic SHANK3 is required for mature astrocyte architecture and sensory coding in mouse somatosensory cortex. Using astrocyte-specific viral manipulation in Shank3 mutant and conditional mice, combined with 2D and 3D astrocyte reconstruction, ultrastructural analysis, *in vivo* two photon calcium imaging, astrocyte and neuron co-imaging during sensory stimulation, molecular analysis, and tactile behavior, we examined how early disruption or restoration of astrocytic SHANK3 affects adult circuit function.
Loss of SHANK3 did not simply arrest astrocyte maturation. Instead, adult astrocytes showed a paradoxical remodeling phenotype: increased volume, branch complexity, and primary-branch hypertrophy, but reduced contact with presynaptic domains. This mismatch suggests that astrocytes expand without appropriately allocating fine processes to synaptic sites. Consistent with this disorganization, astrocytic Ca^{2+} signaling was altered across microdomains, branches, and somata. During sensory stimulation in awake animals, neuronal responses were more frequent but less reproducible, with reduced trial-by-trial reliability and lower response amplitude similarity. Astrocyte-neuron temporal coupling was also weakened, indicating impaired coordination of glial and neuronal activity. Reduced expression of astrocytic glutamate and GABA transporters further suggested compromised local neurotransmitter regulation.
Restoring SHANK3 selectively in astrocytes during the early postnatal period rescued astrocyte architecture, compartmental Ca^{2+} signaling, neuronal reliability, astrocyte-neuron coupling, transporter expression, and tactile allodynia, whereas adult restoration was insufficient. These results support a model in which developmental astrocytic SHANK3 functions as a maturation checkpoint that aligns astrocyte process organization, neurotransmitter homeostasis, and neuron-glia timing to stabilize sensory coding in adulthood.

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Poster

PSTR044: Structural Plasticity and Extracellular Matrix Dynamics

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Topic: B.05. Synaptic Plasticity

Support: NIH-NINDS Grant R01NS146406
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NIH-NIDCD Grant R01DC019380

Title: Tilt-in-place two-photon imaging reveals unreliable vestibular cortical coding in Shank3$^{-/-}$ mice

Authors: *D. ZHOU, J. J. KIM, S. G. SADEGHI, T. DEEMYAD;
Dept. of Otolaryngology-Head and Neck Surgery, Johns Hopkins Univ., Baltimore, MD

Abstract: Vestibular dysfunction and imbalance are common in autism spectrum disorder (ASD), yet little is known about how ASD-associated mutations affect cortical representations of self-motion. Progress has been limited by the difficulty of imaging identified neuronal populations during controlled vestibular stimulation. We adapted tilt-in-place microscopy (TIPM) for mice to test whether naturalistic body tilt evokes reliable vestibular cortical activity and whether this representation is altered in Shank3$^{-/-}$ mice, a genetic model of ASD.
Neonatal mice received bilateral AAV-mediated expression of jRGECO1a in layer 2/3 neurons of retrosplenial and posterior parietal cortices, regions that receive vestibular input. At 3-4 weeks, mice were implanted with cranial windows, head-fixed in a custom body holder mounted to a servo-controlled rotation stage and subjected to repeated 20° nose-down tilts. To avoid motion artifacts, calcium activity was imaged during baseline and immediately after rapid return to horizontal. Tilt-responsive neurons were identified across repeated trials using Suite2p and custom Python analysis.
In wild-type mice, TIPM evoked stereotyped increases in cortical calcium activity across trials, demonstrating that this approach can resolve reproducible vestibular cortical responses. In Shank3$^{-/-}$ mice, however, tilt-responsive neurons showed reduced peak calcium amplitudes, fewer responsive neurons, and lower trial-to-trial response reliability. Shank3$^{-/-}$ cortical responses also showed reduced correlation with the timing of return-to-horizontal, increased inter-trial coefficient of variation, and faster decay kinetics. At the population level, Shank3$^{-/-}$ vestibular cortices exhibited increased event frequency but reduced response amplitude, suggesting a shift from reliable stimulus-locked coding toward noisier, less stable activity.
These findings establish TIPM as an accessible platform for repeated two-photon imaging of vestibular cortical responses in mice. More importantly, they indicate that SHANK3 loss disrupts the reliability and temporal structure of cortical vestibular representations, providing a potential circuit-level mechanism linking ASD-associated gene mutations to vestibular imbalance and altered self-motion processing.

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Poster

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Title: Convergent astrocyte remodeling at tripartite synapses in Cntnap2 and Shank3 mouse models of autism

Authors: *Y. CHEN, J. J. KIM, S. DILLON, N. HARDING, X. DENG, S. G. SADEGHI, T. DEEMYAD;
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Abstract: ASD risk genes are diverse, yet sensory phenotypes often converge. Prior comparisons of Cntnap2 and Shank3 deficient mice found shared sensory-evoked response impairments despite distinct molecular functions, suggesting common circuit-level consequences across genetic models. Because astrocytes shape synaptic maturation, neurotransmitter clearance, and perisynaptic organization, we asked whether Cntnap2 and Shank3 loss converge at astrocyte morphology and tripartite synapse structure in sensory cortex. We analyzed adult somatosensory cortex of wild-type, Cntnap2-/-, and Shank3-/- mice using immunohistochemistry-based astrocyte labeling and 2D and 3D reconstruction, Sholl and fractal analyses, electron microscopy to assess astrocyte contact with pre and postsynaptic compartments, and qPCR for astrocytic synapse-regulatory genes, including glutamate and GABA transporters. In Shank3-/- mice, astrocytes showed enlarged domains, increased branch complexity, and hypertrophy of primary processes, but electron microscopy revealed reduced astrocyte engagement with presynaptic domains, indicating disorganized expansion rather than functional perisynaptic maturation. qPCR showed altered expression of GLT-1, GLAST, and GAT-3, consistent with impaired local neurotransmitter regulation. Immunohistochemical analysis in Cntnap2-/- mice revealed a similar morphological phenotype, including increased astrocyte structural complexity and altered fine-process organization. Comparative electron microscopy and molecular analyses are being used to determine whether this shared astrocyte remodeling corresponds to convergent defects in tripartite synapse architecture and transporter expression, or whether each gene produces distinct synaptic-glial signatures. Together, these data support a model in which molecularly distinct ASD-associated mutations converge on astrocyte remodeling, while the functional consequence of that remodeling depends on whether fine perisynaptic processes are properly positioned at synaptic domains. This work reframes astrocyte hypertrophy in ASD models as a potential defect in synaptic targeting and neurotransmitter homeostasis, rather than simply reactive gliosis or delayed maturation.

Disclosures: Y. Chen: None. **J.J. Kim:** None. **S. Dillon:** None. **N. Harding:** None. **X. Deng:** None. **S.G. Sadeghi:** None. **T. Deemyad:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

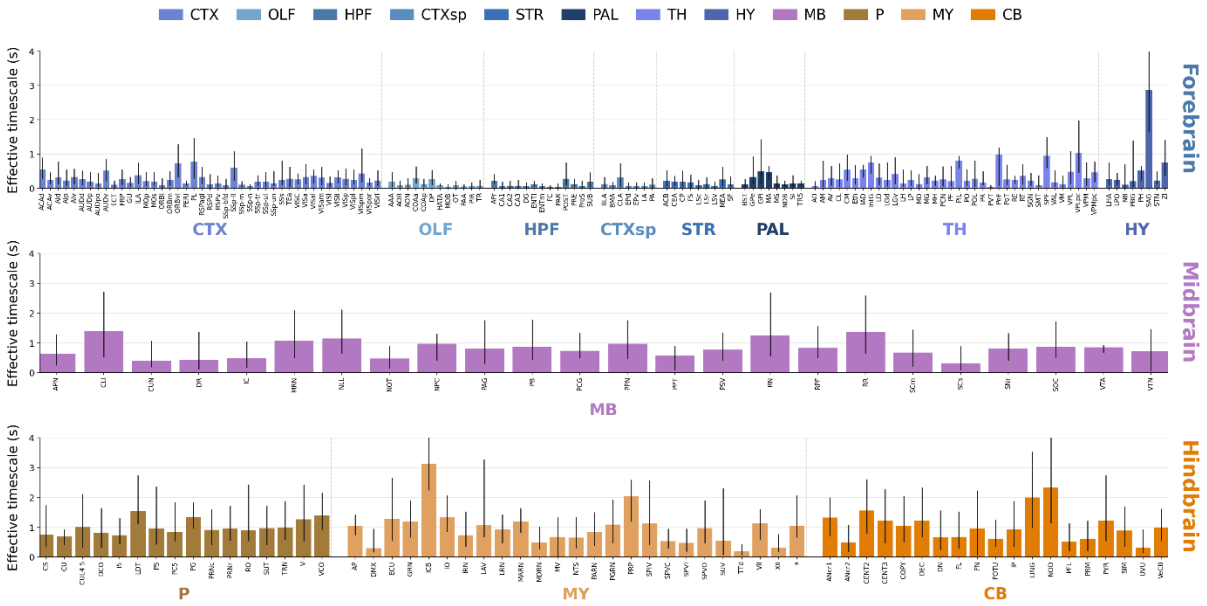
Program #/Poster #: PSTR045.01/N1

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

Title: A Brain-Wide Atlas of Intrinsic Neural Timescales in Mice

Authors: *K. B. STAFFORD[1], S. GÜLENÇ[2], Z. YANG[3], V. BISANI[4], J. M. MANLEY[5]; [1]Electrical Engin., Univ. of New Brunswick, Fredericton, NB, Canada; [2]Yildiz Tech. Univ., Istanbul, Turkey; [3]The Hong Kong Univ. of Sci. and Technol., Sai Kung District, Hong Kong; [4]Independent Researcher, Chennai, India; [5]Neuromatch Acad., Beaverton, OR

Abstract: Understanding how the brain integrates information requires a shift from localized functional studies to mapping a brain-wide temporal architecture. Intrinsic neural timescales (ITs), defined as the decay time constant of a neuron's spontaneous spiking autocorrelation, provide a quantitative proxy for how long a local circuit retains information about its recent activity. Yet their accurate estimation has historically been limited by computational biases in spike train analysis and the oversimplified assumption that each neuron operates on a single characteristic timescale. In this study, we address these limitations by applying a hybrid framework combining the unbinned intrinsic Spike Time Tiling Coefficient (iSTTC) autocorrelation estimator with Bayesian Information Criterion (BIC)-guided multi-exponential modeling to 89,047 single units across 266 mouse brain regions, drawn from 580,598 recorded units across 427 sessions and 131 mice in the IBL 2025 Brainwide Map Release. We reveal a robust rostro-caudal hierarchy of intrinsic neural timescales across 220 brain regions, with median effective timescales approximately 4.5-fold longer in the hindbrain (956 ms) than in the forebrain (213 ms), spanning nearly two orders of magnitude (37.9-3,115 ms). This gradient held within 100% of individual mice tested and was supported by a Bayesian hierarchical model controlling for mouse, session, and probe identity. We further demonstrate that 73.9% of neurons are better described by multi-component models, and that fast (τ_1) and slow (τ_2) dynamical modes co-vary sublinearly across regions (log-log slope=0.545, r=0.766), suggesting distinct cellular and network origins. These findings provide the most comprehensive brain-wide timescale atlas to date and lay the groundwork for linking single-neuron dynamics to population-level representations required for decision making and adaptive behavior.



Disclosures: K.B. Stafford: None. **S. Gülenç:** None. **Z. Yang:** None. **V. Bisani:** None. **J.M. Manley:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.02/N2

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

Title: CA1 pyramidal neurons are hypoexcitable in a mouse model of chronic hyperglycemia

Authors: *B. BALSAMO[1], A. MARRON[3], D. H. BRAGER[2];
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Abstract: Diabetes is increasingly recognized to not only affect metabolism, but to also significantly impact the central nervous system. As a result of this shift, cognitive impairments associated with diabetes are gaining increasing attention. Growing evidence links both type 1 and type 2 diabetes to deficits in learning, memory, executive function, mood, and an increased risk of dementia. Multiple studies found structural and functional brain abnormalities in diabetic individuals, with vulnerability observed in regions critical for cognition and learning and memory, including the hippocampus. The hippocampus, a brain region critical for learning and memory, is particularly vulnerable to metabolic insults. However, the cellular and molecular

mechanisms through which chronic metabolic dysfunction leads to neuronal damage and neural circuit impairment remain poorly understood. We investigated the impact of chronic hyperglycemia on the neurophysiology of CA1 pyramidal neurons in the hippocampus using whole cell recording. Acute hippocampal slices were made from control mice and mice treated with streptozotocin (STZ) to model chronic hyperglycemia. We found that CA1 neurons from hyperglycemic mice fired fewer action potentials for a given amount of injected current compared to control mice. This was due, in part, to the lower input resistance of CA1 neurons from chronic hyperglycemic mice. We found that there were no differences in action potential properties (e.g., threshold) between the groups. The underlying mechanism of this hypoexcitability and the impact on synaptic plasticity are currently under investigation. By elucidating how hyperglycemia alters hippocampal excitability and synaptic plasticity, this study will identify cellular mechanisms by which hyperglycemia contributes to cognitive impairment.

Disclosures: B. Balsamo: None. **A. Marron:** None. **D.H. Brager:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.03/N3

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

Title: Sublaminar and physiological diversity of layer 5 corticocallosal neurons across mouse cortical areas

Authors: *K. LEE[1,2], S. P. BROWN[4,5], J. KIM[3,4,6,7];
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Abstract: Layer 5 (L5) of the neocortex contains diverse projection neuron types, including intratelencephalic (IT) and pyramidal tract (PT) neurons. Although PT neuron diversity has been relatively well characterized, heterogeneity among L5 IT-type neurons remains less clear. Here, we investigated the sublaminar organization and physiological diversity of corticocallosal neurons (CCNs), a representative IT-type population, across the motor, somatosensory, and visual cortices (MC, SC, and VC) of mice.Using retrograde labeling, Rbp4-Cre mice, molecular sublayer profiling, and whole-cell patch-clamp recordings, we found that CCNs in the MC and SC segregated into two distinct sublayers, L5a and L5b. These sublayers differed in Rbp4-Cre expression and intrinsic excitability. Notably, the direction and extent of these physiological differences varied by cortical area. Unlike the MC and SC, the VC displayed a tripartite L5 organization composed of top, middle, and bottom sublayers with distinct cellular composition and physiological properties. Top and bottom VC CCNs showed largely similar molecular

profiles and excitability but differed in short-term synaptic dynamics. These results reveal that L5 CCNs are not a uniform IT-type population, but instead exhibit cortical area-specific sublaminar organization and physiological specialization. This study also provides useful cellular-level information for interpreting and using the Rbp4-Cre mouse line, a widely used genetic tool for targeting L5 neurons.

Disclosures: K. Lee: None. **S.P. Brown:** None. **J. Kim:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.04/N4

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

Support: NIH NS132590, (SMD)
NIH NS118731 (SMD)
NIH NS133338 (SMD)
NIH MH116003 (SMD)

Title: Regulation of CeA tonic currents by GluD1: relevance to inflammatory pain

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Abstract: GluD1 is an unusual iGluR, which has been considered orphan for a long time due to lack of typical ligand-gated ion channel current. Our recent study demonstrated phasic responses mediated by acetylcholine in the dorsal striatum medium spiny neurons that are GluD1-dependent suggest that GluD1 may function as a ion channel with acetylcholine as the cognate receptor. Several recent studies have also found tonic currents mediated through GluD1 in various brain regions. However, additional characterization of these tonic currents and relevance to disease states is lacking. We investigated the contribution of GluD1 to tonic currents in the central amygdala (CeA) which is enriched in GluD1 under both normal and inflammatory pain conditions. NASPM, a blocker of the GluD1 ion channel pore, reduced the leak currents in wild-type but not in GluD1 KO CeA neurons in the presence of AMPA, NMDA and GABAA antagonists, suggesting GluD1-mediated tonic currents. In current-clamp recordings, NASPM lead to hyperpolarization in WT but not in GluD1 KO mice suggesting a role of GluD1 in maintaining resting membrane potential. Furthermore, GluD1 KO CeA neurons showed hyperexcitability, characterized by increased action potential generation and reduced rheobase. The tonic current and excitability characteristics in GluD1 KO were mimicked in wild-type mice with CFA-induced inflammatory pain consistent with the downregulation of GluD1 observed in CFA model. In both GluD1 KO and CFA model, reduced pERK was found to contribute to

hyperexcitability since incubation of WT brain slices with ERK inhibitor increased the excitability to GluD1 KO level. We finally further characterised the structure-function mechanism underlying GluD1-mediated tonic currents. Incubation of slices with D-serine did not affect baseline leak currents or the overall NASPM inhibition. In contrast, incubation with Cbln1 led to a reduction in NASPM-sensitive currents. Our
results identify a unique contribution of tonically active GluD1 in regulating CeA neuron baseline activity and excitability and relevance to inflammatory pain. These results also identify novel structure-function features that may contribute to GluD1-mediated tonic currents.

Disclosures: P.K. Kola: None. **S.M. Dravid:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.05/N5

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

Support: NIH Grant MH131570
Dr. John J. Kopchick Fellowship

Title: Synaptic mechanisms integrating prelimbic and paraventricular thalamic inputs in local networks of the anteroventral thalamic reticular nucleus

Authors: *D. JALLOUL[1,2], G. AQUINO-MIRANDA[1], F. H. DO MONTE[1,2], M. BEIERLEIN[1,2];
[1]McGovern Med. Sch. at UTHealth Houston, Houston, TX; [2]The Univ. of Texas MD Anderson Cancer Ctr. UTHealth Houston Grad. Sch. of Biomed. Sci., Houston, TX

Abstract: The thalamic reticular nucleus (TRN) regulates thalamocortical communication by integrating cortical and thalamic synaptic inputs and providing inhibitory control over other thalamic nuclei. The limbic anteroventral TRN (avTRN) governs decision-making and adaptive behaviors, which are often disrupted in neuropsychiatric disorders such as addiction and depression. The avTRN receives convergent glutamatergic inputs from the prelimbic cortex (PL) and the paraventricular thalamic nucleus (PVT). However, the synaptic and cellular mechanisms by which these inputs are integrated in the avTRN remain unclear. To address this question, we combined optogenetics and whole-cell recordings in thalamic brain slices derived from adult male rats. We found that avTRN neurons exhibited weak or absent burst firing, unlike the robust burst firing characteristic of sensory TRN. Photoactivation of PL inputs with brief stimulus trains evoked excitatory postsynaptic responses that display short-term synaptic facilitation in avTRN. Conversely, photoactivation of PVT inputs evoked large-amplitude, all-or-none excitatory responses that led to precise action potential firing and displayed short-term synaptic depression in avTRN. Next, we used pharmacological approaches to assess the contribution of dendritic T-

type calcium channels to synaptic integration in avTRN. Blockade of T-type calcium channels substantially reduced synaptically evoked firing (PL: 54.7%, n=7; PVT: 34% n=5). Unexpectedly, activation of either PL or PVT inputs evoked inhibitory postsynaptic responses in a subset of TRN neurons that were sensitive to AMPA and GABA-A receptor antagonists, suggesting that both pathways recruit feedforward inhibition within avTRN. Consistent with this interpretation, optogenetic activation of local avTRN axons evoked large inhibitory responses that exhibited short-term synaptic depression, demonstrating functional inhibitory connectivity within avTRN. Our results suggest that PL and PVT inputs display distinct temporal dynamics in avTRN, and that T-type calcium channels amplify synaptic signaling in both pathways. In addition, the recruitment of feedforward inhibition by both PL and PVT inputs, together with evidence of local inhibitory synaptic connections, reveals a previously unrecognized inhibitory circuit within the avTRN that may dynamically regulate limbic thalamocortical communication.

Disclosures: D. Jalloul: None. **G. Aquino-Miranda:** None. **F.H. Do Monte:** None. **M. Beierlein:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.06/N6

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

Support: DE018661

Title: Characterization of Electrophysiological Properties of SMR2-Expressing Trigeminal Ganglion Neurons in Mice

Authors: *A. R. SHARMA[1], S. GUPTA[2,3], J. G. GU[4];
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Abstract: Characterization of Electrophysiological Properties of SMR2-Expressing Trigeminal Ganglion Neurons in Mice
Amit Raj Sharma, Sourav Gupta, Jennifer Ling, Jianguo G. Gu
Introduction: Aδ-afferent neurons in the trigeminal ganglion (TG) mediate nociceptive and innocuous sensory signaling and may contribute to pathological pain. Recent transcriptomic studies identified submaxillary gland androgen-regulated protein 2 (SMR2) as a marker of Aδ-afferent nociceptors in dorsal root ganglia; however, the functional properties of SMR2-expressing TG neurons remain unknown. We generated transgenic mice expressing ChR2/eYFP in SMR2-positive neurons and characterized their electrophysiological and chemosensory properties.
Methods: SMR2-Cre mice were crossed with Ai32 reporter mice to generate SMR2$^{ChR2/eYFP}$

mice. TG neurons were identified by eYFP fluorescence and studied using whole-cell patch-clamp recordings in an ex vivo TG preparation. Intrinsic membrane properties, voltage-activated currents, conduction velocity (CV), and responses to ATP (2 mM), GABA (2 mM), and acidic solution (pH 5.0) were examined. Single-cell RT-PCR was performed to assess expression of SMR2 and Nav1.8.
Results: $SMR2^{ChR2/eYFP}$ neurons were present in both sexes and exhibited CVs of 2–9 m/s, consistent with Aδ-afferents. Soma diameters ranged from 23–35 μm. Based on action potential (AP) characteristics, 70% of neurons were classified as nociceptors and 30% as non-nociceptors. Compared with non-nociceptors, nociceptive neurons displayed greater membrane capacitance, lower input resistance, higher rheobase, larger AP amplitude, and less negative AP threshold. Densities of voltage-activated inward and outward currents were significantly lower in nociceptive neurons. Mechanically activated currents were robust in non-nociceptive neurons but absent in nociceptive neurons. ATP- and GABA-evoked currents were significantly larger in non-nociceptive neurons, whereas proton-evoked currents were significantly larger in nociceptive neurons. Single-cell RT-PCR confirmed co-expression of SMR2 and the nociceptive marker Nav1.8 in a subset of SMR2-positive neurons.
Conclusions: SMR2-expressing TG neurons represent a distinct population of Aδ-afferents composed predominantly of nociceptors with a smaller non-nociceptive subset. These subpopulations differ in membrane properties, voltage-gated currents, and mechanical and chemical sensitivities. The findings establish a functional framework for investigating the contribution of SMR2-expressing trigeminal Aδ-afferents to sensory processing and pain mechanisms.

Disclosures: A.R. Sharma: None. **S. Gupta:** None. **J.G. Gu:** A. Employment/Salary (full or part-time):; Professor, UAB. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; PI, NIH Research Grant RO-1.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.07/N7

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

Support: R90DA060341

Title: Cell Type Specific Effects of Bmal1 Knockout on Physiological properties of neocortical pyramidal neurons

Authors: *E. N. SIEGER[1], E. RAGONE[2], J. LEE[2], E. BARRIOS[3], S. B. NELSON[4];
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[4]Dept Biol MS#008, Brandeis Univ., Waltham, MA

Abstract: Bmal1 and other circadian transcription factors are thought to regulate cortical excitability in the context of epilepsy and psychiatric disease, but the underlying physiological mechanisms are not well understood. We found that conditional knockout (cKO) of Bmal1 in forebrain excitatory progenitor neurons produced distinct changes in the intrinsic excitability of different pyramidal neuron subtypes. Layer 5 Intratelencephalic (L5 IT) neurons' excitability increased (.0658 Hz/pA WT, n=17 to .0848 Hz/pA, n=21), while Layer 5 Extratelencephalic (L5 ET) neurons' excitability decreased (.0928 Hz/pA, n=15 to .076 Hz/pA, n=12), and excitability of Layer 2/3 Intratelencephalic (L2/3 IT) neurons' was unchanged (.0517 Hz/pA, n=9 to .0502 Hz/pA, n=12). There was an increase in the input resistance of both L5 IT (158.2 MΩ WT to 194.7 MΩ) and L2/3 IT (123.7 MΩ WT to 153.5 MΩ) neurons, while the input resistance was decreased in L5 ET (98 MΩ WT to 82.2 MΩ) neurons. IT neurons display prolonged spike frequency adaptation and have a long lasting post train afterhyperpolarization, both of which are reduced by the KO. Due to Bmal1's known function in regulating circadian rhythms, we decided to investigate whether these cell types exhibited time dependent changes in their excitability. L5 ET neurons display a circadian change in excitability (.0928 Hz/pA Day and .0628 Hz/pA Night) and input resistance (98 MΩ Day and 82.9 MΩ Night), while L5 ET neurons in cKO mice do not have circadian changes in excitability (.076 Hz/pA Day and .0753 Hz/pA Night) or input resistance (82.2 MΩ Day and 85.8 MΩ Night). Circadian changes in excitability were more muted in L5 IT neurons (.0658 Hz/pA Day and .0643 Hz/pA Night), although there was a small decrease in input resistance (158.2 MΩ Day and 127.9 MΩ Night). The cKO results in a loss of callosal projections by both L5 and L2/3 IT neurons. We also replicated the physiological effects on excitability in L5 pyramidal neurons with a postnatal injection of viral Cre, showing the effects are not caused by changes during prenatal development. As in other brain regions, cKO leads to cortical hyperactivation of the mTOR pathway, a signaling pathway strongly implicated in regulation of cortical excitability. The increased excitability of L5 IT neurons may contribute to the reduced seizure threshold seen in these mice.

Disclosures: E.N. sieger: None. **E. Ragone:** None. **J. Lee:** None. **E. Barrios:** None. **S.B. Nelson:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.08/N8

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

Title: The role of adisrupted G protein-coupled receptor in mouse brain:From an electrophysiological perspective

Authors: *Y.-H. LEE[1], H.-S. HUANG[2];
[1]Natl. Taiwan Univ., Zhongzheng Dist., Taipei City, Taiwan; [2]Natl. Taiwan Univ., Taipei, Taiwan

Abstract: According to the World Health Organization (WHO), nearly one in seven individuals worldwide is affected by a mental health condition. It has been known that neuropsychiatric disorders can be heritable, including Schizophrenia, Bipolar disorder, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, etc. Consequently, a growing body of evidence emphasizes the complex genetic architecture driving susceptibility to these conditions. In this study, we identified a stop-gain variant within an angiotensin receptor, a class of G protein-coupled receptors (GPCRs), which leads to potential psychiatric-related behavior deficit. Although the protein function is not yet fully understood, previous research has shown that it might be associated with programmed cell death and apoptosis. Furthermore, it is confirmed to be expressed in the adult human brain, suggesting a potential role in neural function. Several clinical studies have revealed that mutations in this gene might result in neuropsychiatric deficiencies, including impaired learning memory, as well as anxiety-like behavior. To fully uncover the impact of this specific gene on brain function, we previously evaluated excitatory neuron-specific conditional knockout (cKO) mice and observed potential psychiatric-related behavioral deficits. Given that the medial prefrontal cortex (mPFC) is a key region linked to these behaviors, we performed whole-cell patch-clamp electrophysiology to investigate cellular and synaptic alterations in the pyramidal neurons of these cKO mice and their corresponding controls. Our results revealed significant functional dysregulation in these neurons, supporting a role for this receptor in prefrontal networks.

Disclosures: Y. Lee: None. **H. Huang:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.09/O1

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

Support: NICHD Intramural Award to CJB

Title: Cross-species electrophysiological comparison of fast-spiking inhibitory neurons across multiple brain regions

Authors: *L. T. HEWITT[1], V. K. CHITTAJALLU[2], A. CACCAVANO[3], G. A. VARGISH[4], G. PIZZIRUSSO[5], A. VLACHOS[6], N. MCLEAN[6], X. YUAN[7], K. A. ZAGHLOUL[10], B. B. AVERBECK[11], K. A. PELKEY[8], C. J. MCBAIN[9];
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on Cell. and Synaptic Physiol., [5]NICHD, Bethesda, MD; [6]NICHD/NIH, Bethesda, MD; [7]NIH, Bethesda, MD; [8]NICHD/LCSN, NIH, Silver Spring, MD; [9]Lab. Cell/Molec Neurosci, NIH, Bethesda, MD; [10]NINDS, Bethesda, MD; [11]NIMH/NIH, Bethesda, MD

Abstract: Mouse models have been historically used in neuroscience research to determine potential therapeutic targets for human neurophysiological disease. However, there is a surprising lack of literature describing the overlap in the underlying function of mouse neurons compared to other species, including non-human primates and humans. It has become increasingly valuable to characterize similarities and innovations in non-human primate and human brain tissue in comparison to the rodent to determine the translational relevance of mouse physiology. Inhibitory neurons are vastly diverse and exhibit numerous sub-types, each providing exquisite spatio-temporal control over network dynamics. The sparse representation of GABAergic neuron subtypes has made them inherently difficult to study without targeted labeling through genetic/molecular approaches. Immense amounts of research indicate these inhibitory neurons are altered in disease states in the mouse brain; however, whether these neurons exhibit similar aberrant and baseline properties in humans and non-human primates is poorly understood. We investigated intrinsic properties using regional specific injections of the virus S5E2, which selectively labels fast-spiking (FS) parvalbumin neurons, in tandem with ex-vivo whole-cell patch clamp electrophysiology recordings. We recorded FS neurons in hippocampus and cortex across three species: mouse, macaque, and humans, in addition to recordings of striatal FS neurons in the mouse and macaque. Intrinsic electrophysiological properties from these experiments were placed in a non-biased k-means clustering algorithm to determine if regional and species dependent differences result in separation of FS neurons into discrete clusters. Recordings from humans, macaque, and mouse in the hippocampus and cortex divide into reliable populations of species-specific clusters. Data from mouse and macaque recordings in the striatum reveal a separation of mouse and macaque FS neurons. We also tested the intrinsic integration properties of FS neurons across species and regions using a simulated inhibitory input ‘pause’ protocol. Mouse FS neurons reliably exhibit a pause in high frequency firing in response to the pause protocol in the hippocampus, cortex, and striatum. Interestingly, macaque FS neurons do not exhibit the same pause response in the hippocampus and cortex. However, striatal FS neurons in the macaque do show a pause of high frequency firing. Our data indicate the convergence and divergence of physiological properties exist in region and species dependent manners.

Disclosures: L.T. Hewitt: None. **V.K. Chittajallu:** None. **A. Caccavano:** None. **G.A. Vargish:** None. **G. Pizzirusso:** None. **A. Vlachos:** None. **N. McLean:** None. **X. Yuan:** None. **K.A. Zaghloul:** None. **B.B. Averbeck:** None. **K.A. Pelkey:** None. **C.J. McBain:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.10/O2

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

Title: Characterizing LAMP5+ neurogliaform cells across regions and species using a novel enhancer AAV.

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Abstract: Subpopulations of cortical GABAergic interneurons (INs) are diverse, exhibiting distinct anatomical, molecular, and functional characteristics. While numerically sparse, these minority populations critically balance excitation to coordinate network activity. Lysosome-associated membrane protein-5 (LAMP5)- expressing neurogliaform cells (NGFCs) represent one cardinal class of INs found throughout the hippocampus, neocortex, and striatum. NGFCs uniquely provide slow volume transmission across their dense axonal arborizations at synaptic and extrasynaptic sites through activation of both inotropic $GABA_A$ and metabotropic $GABA_B$ receptors. These unusual transmission characteristics combined with their extensive electrical/chemical interconnectivity and propensity to barrage fire optimally position NGFCs to coordinate inhibitory network influence over circuit activity broadly across space and time. Indeed, NGFCs have been implicated in slow network rhythms such as up/down state transitions and theta oscillations as well as providing slow GABAergic trophic support for immature neuron circuit integration following adult neurogenesis. Efficient targeting of NGFCs is confounded by the need for time-consuming intersectional genetics that remain limited to mice. Recombinant adeno-associated viruses (rAAVs) with small DNA regulatory elements identified with ATAC-Seq (Enhancer-AAVs) provide a novel method for cell-type specific targeting, allowing the identification and manipulation of neurons across species. However, enhancer-AAV specificity for intended target cell populations varies across brain regions, delivery method, and development. We compared transgene expression driven by the novel LAMP5 IN enhancer BiLAMP5e3 in mouse hippocampus, cortex, and striatum delivered by intracranial stereotax injection (IC, focused) or retro-orbitally (RO, systemic) to adult mice and by intracerebroventricular injection (ICV, systemic) perinatally. Additionally, AAV-PHP.eB-BiLAMP5e3-dTom was IC delivered to the hippocampus of non-human primates (NHPs) for cross-species comparisons. We'll report on the specificity of AAV-PHP.eB-BiLAMP5e3-dTom for NGFCs across regions, species, and development based on combined immunohistochemical, morphological, and electrophysiological profiling of dTom expressing cells. Our findings reveal best practices to maintain AAV-PHP.eB-BiLAMP5e3-dTom specificity for NGFCs and highlight region and species divergence of NGFC electrical properties.

Disclosures: N. McLean: None. **L.T. Hewitt:** None. **A. Vlachos:** None. **A. Caccavano:** None. **E. Furlanis:** None. **S. Hunt:** None. **X. Yuan:** None. **K.A. Pelkey:** None. **C.J. McBain:** None. **P. Harmon:** None. **A. Cummins:** None. **R. Azadi:** None. **B.B. Averbeck:** None. **Y. Wang:** None. **G.J. Fishell:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.11/O3

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

Support: NIA Grant R01AG093992-01
NIA Grant R21AG067029
Virginia Center on Ageing's - Alzheimer's and Related Diseases Research Award Fund Grant AAG 26-02

Title: Characterization of the single-channel properties of α7-containing nicotinic acetylcholine receptors expressed on basal forebrain cholinergic neurons

Authors: *D. DRACH[1], S. BIRADAR[1], A. A. GEORGE[2];
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Abstract: Alzheimer's disease (AD) is the most common cause of dementia with roughly 5.1 million Americans suffering from the disease. AD is a neurodegenerative disease linked to the build-up of insoluble amyloid-beta (Aβ), development of neurofibrillary tangles, and neurodegeneration. Basal forebrain cholinergic neurons (BFCNs) are particularly vulnerable to the toxic effects of oligomeric $A\beta_{1\text{-}42}$ ($oA\beta_{42}$). Multiple studies now suggest that elevated levels of soluble $oA\beta_{42}$, rather than insoluble Aβ plaques, drive the selective degeneration of BFCNs, serving as the strongest predictor of cognitive decline in AD. However, the mechanisms contributing to $oA\beta_{42}$-induced BFCN loss is unknown. Synaptic transmission and neuronal intrinsic excitability in the mammalian brain are mediated by α7-containing nicotinic acetylcholine receptors (α7-nAChRs). In most areas, α7-nAChRs are expressed as homopentameric receptors. However, a small fraction of α7-nAChRs also contain β2 subunits (α7β2-nAChRs). These heteromeric channels have been confirmed to form functional receptors and are highly sensitive to modulation by $oA\beta_{42}$. Our published findings have shown that naturally occurring Aβ peptide fragments can activate and preferentially modulate the single-channel properties of α7- and α7β2-nAChRs when expressed in heterologous systems. We have expanded on our previous work by examining the effects of $oA\beta_{42}$, the N-Aβ fragment, and the N-Aβ core on the single-channel properties of α7*-nAChRs (*indicating multiple stoichiometries) expressed on BFCNs using the ChAT(BAC)-eGFP transgenic mouse model. Using cell-attached single-channel electrophysiology, we provide evidence for the first time that both the $N\text{-}A\beta_{1\text{-}15}$ fragment [$N\text{-}A\beta_{1\text{-}15}$; 1 uM], and its $N\text{-}A\beta core_{10\text{-}15}$ hexapeptide [$N\text{-}A\beta core_{10\text{-}15}$; 1 uM] elicit BFCN single-channel events when administered exclusively. Both the $N\text{-}A\beta_{1\text{-}15}$ or $N\text{-}A\beta core_{10\text{-}15}$ fragments enhanced α7*-nAChR single-channel amplitude and burst duration when compared to the α7*-nAChR selective agonist choline. To validate BFCN α7*-nAChRs single-channel events, co-administration of $N\text{-}A\beta_{1\text{-}15}$ or $N\text{-}A\beta core_{10\text{-}15}$ with the α7*-nAChRs selective positive allosteric modulator PNU-120596 significantly enhanced α7*-nAChR single-channel

burst duration and open-dwell-times within bursts compared to N-Aβ_{1-15} or the N-Aβcore$_{10-15}$ alone. These findings provide new insights into the mechanisms by which amyloid peptides modulate α7*-nAChR function and identify potential therapeutic strategies for targeting specific α7*-nAChR subtypes to preserve BFCN function and mitigate oAβ_{42}-induced neuronal instability during the preclinical stages of AD.

Disclosures: D. Drach: None. **S. Biradar:** None. **A.A. George:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.12/O4

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

Support: National Research Foundation of Korea Ministry of Education Grant RS-2025-00517742

Title: An interpretable gene-program framework for within-cell-type electrophysiological variation in Patch-seq neurons

Authors: *C. HEO, S.-M. PARK;
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Abstract: Neurons of the same transcriptomic cell type can differ markedly in intrinsic excitability, yet the molecular basis of this within-type variation remains largely uncharacterized. Here, we demonstrate that this residual electrophysiological variation is shaped by phenotype-specific gene modules, concentrated in distinct excitability phenotypes and recoverable from electrophysiology-relevant gene programs. We analyzed 3,729 Patch-seq neurons across 47 electrophysiological targets. After separating dominant cell-types, residual predictability was highly non-uniform. Signal concentrated in spike waveform and threshold, passive membrane and hyperpolarization, firing response, and latency-related phenotypes — suggesting that within-type excitability variation contains phenotype-specific molecular structure rather than only imperfect cell-type classification or measurement noise. To identify candidate programs, we developed a sparse, interpretable framework centered on an electrophysiology-relevant hypothesis space spanning ion channels, auxiliary subunits, transporters, receptors, trafficking genes, and residual-associated genes selected from training data only. ElasticNet-based models achieved median R^2 of 0.511, a 3.1-fold improvement over an unstructured nonlinear baseline. Electrophysiology-relevant genes preserved more signal than transcriptome PCA, supporting their use as an interpretable molecular search space. Phenotype-specific importance profiles nominated partially distinct programs across targets. Beyond core channel genes, auxiliary subunit, trafficking, and transcriptional regulatory programs contributed differentially across phenotypes. Spike waveform and threshold features were enriched in fast-inactivating K- and

Na-channel programs, whereas hyperpolarization and passive properties emphasized membrane transporter and ion pump programs. Firing response and latency features additionally recruited ionotropic receptor and activity-dependent regulatory candidates, suggesting that within-type excitability is organized along partially non-overlapping functional axes rather than a single ion-channel gradient. These findings frame within-type excitability as a phenotype-specific gene-program problem rather than a single transcriptomic axis. By organizing residual variation into an inspectable molecular hypothesis space, this framework provides a principled foundation for gene-level perturbation and pathway analysis, and a path toward understanding how excitability-linked gene programs contribute to neuronal diversity and its disruption in disease.

Disclosures: C. Heo: None. **S. Park:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.13/O5

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

Support: DFG Grant 526008379

Title: Neuroplastin and PMCA Shape Cortical Excitability: From Single Neurons to Local Cirtcuits.

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Abstract: Learning and memory recall are encoded within specific neuronal circuits; however, the molecular mechanisms supporting these processes remain largely unknown. Neuroplastin (Nptn), a glycoprotein type I of the immunoglobulin superfamily, plays a key role in synaptic plasticity and memory by stabilizing plasma membrane Ca^{2+} ATPases (PMCA1-4), ultrafast ATP-driven calcium extrusion pumps. Loss of Np reduces PMCA expression and calcium clearance, leading to elevated intracellular Ca^{2+} levels that may impair neuronal function and memory. Previous studies showed that inducible deletion of Nptn after successful training in a visually cued associative memory task causes retrograde amnesia, whereas memory recall remains intact following Nptn deletion in excitatory neurons. This suggests a critical contribution of GABAergic interneurons, which may be particularly vulnerable to calcium dysregulation due

to their high firing rates and brief action potentials. To investigate how Nptn and PMCA regulate cortical activity, electrophysiological recordings were performed across multiple levels of neural organization, from single neurons to neuronal networks and local circuits. Whole-cell current-clamp recordings revealed that $Nptn^{-/-}$ neurons exhibited reduced current-evoked firing and increased calcium-dependent afterhyperpolarization (AHP), a phenotype reproduced in neurons recorded from wild-type mice slices following PMCA inhibition with Carboxyeosin (10 μM). In primary cortical cultures grown on multielectrode arrays (MEAs), pharmacological inhibition of PMCA induced a global increase in firing rate, indicating enhanced network excitability. To identify cell type-specific contributions to circuit activity, acute V1 slices from $Nptn^{-/-}$ and $Nptn^{+/+}$ mice were recorded using high-density MEAs. Putative pyramidal neurons displayed increased firing rates in $Nptn^{-/-}$ mice, particularly in layers 2/3 and 6, whereas putative interneurons showed reduced firing rates, mainly in layers 4 and 6. Together, these findings identify the Nptn-PMCA complex as a key regulator of cortical excitability. Our results support a model in which impaired calcium extrusion enhances AHP, preferentially reduces interneuron firing, and ultimately shifts cortical circuits toward hyperexcitability.

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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.14/O6

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

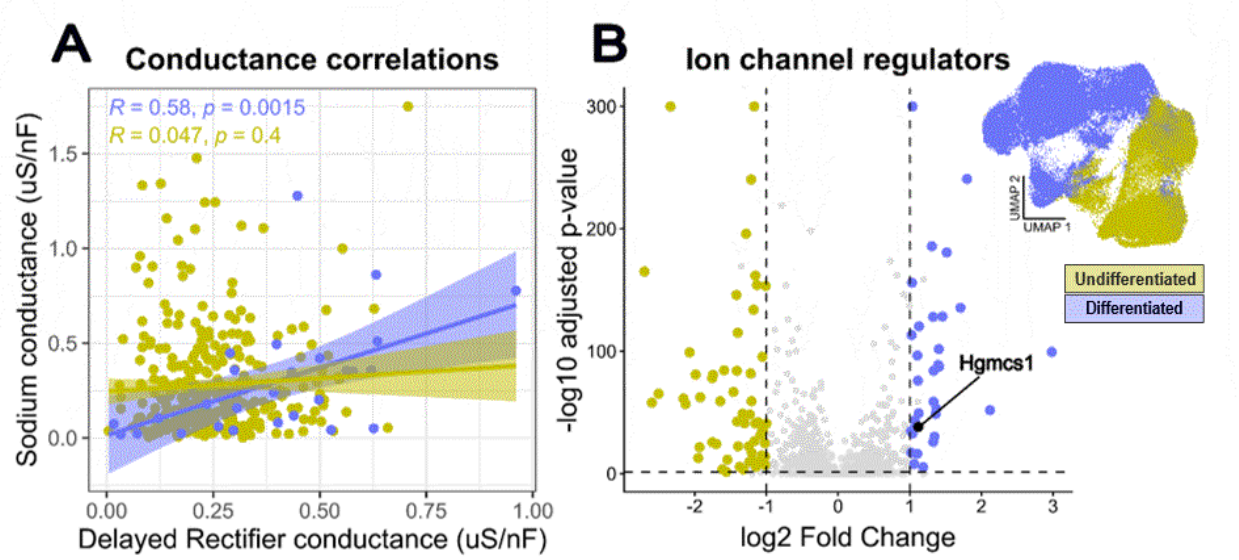
Support: NSF 2320895

Title: Targeted regulation of voltage-gated ion channels in sensory neurons

Authors: *J. R. A. TRINIDAD[1], M. GRAY[2], T. STRASSMAIER[2], R. J. HAEDO[2], J. P. GOLOWASCH[1];
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Abstract: Neuronal activity depends on the coregulated expression of voltage-gated ion channels (VGICs), measured as correlations between different VGICs' RNAs (Fig. A) or conductance levels. The mechanisms that regulate these coexpression patterns are not known. Here, we identified transcriptional programs associated with VGIC correlations in a sensory DRG cell line, F-11. We induced differentiation of F-11 and measured changes in correlations between VGICs using manual and Nanion's high throughput Syncropatch384 automated patch clamp. We observed a significant increase in correlation strength upon differentiation (Fig A INa-IKd: ρ: 0.047→0.578, N: 360). To identify regulators of this VGIC pair, we characterized the transcriptome of F-11 using bulk- and scRNAseq using differential expression analysis and

gene co-expression analysis. We identified groups of highly correlated transcripts called modules that are separated by differentiation state. Modules in differentiated F-11 cells contain transcripts related to VGICs, vesicle trafficking and cholesterol biosynthesis, suggesting that correlations are established at the transcriptome level during differentiation. These regulators involved in cholesterol biosynthesis, such as *Hmgcs1*, promote neuron repair after nerve injury. Surprisingly, these modules of highly correlated genes are also observed in healthy and injured DRG neurons. We selected putative regulators by identifying the differentially expressed transcripts (Fig B). By manipulating these targets, we can test which regulators are necessary for establishing VGIC correlations. We conclude that regulators of VGIC correlations can be identified using co-expression networks.



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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.15/O7

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

Support: NS003135

Title: Examining the Mechanism of Spontaneous Firing in Locus Coeruleus Subpopulations

Authors: *N. L. O'PREY[1], A. BORONAT-GARCÍA[2], Z. M. KHALIQ[3];
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Abstract: The locus coeruleus (LC) is a bilateral nucleus in the dorsal pons and the brain's primary site of noradrenaline (NA)-releasing neurons (NANs). The LC is also one of the first regions to degenerate with aging and in Parkinson's disease (PD). The selective degeneration that LC neurons undergo has been suggested to occur as a result of their spontaneous firing activity. Thus, better knowledge of the LC neurons' electrophysiological properties may be useful to better understand their degeneration in PD. Among the mechanisms contributing to spontaneous activity in other brain regions, the non-selective sodium leak channel NALCN functions to depolarize the resting membrane potential and drives tonic action potential firing. We tested the hypothesis that NALCN contributes to spontaneous activity in LC neurons and thus controls the NA-neurons' baseline excitability. We used mice in which GFP expression is driven by the tyrosine-hydroxylase (TH) promoter, a precursor for NA synthesis and conducted cell-attached and whole-cell patch-clamp recordings on LC-NA neurons to analyze action potential firing properties. We found that lowering extracellular calcium from 2 mM to 0.1 mM substantially increased LC neuron firing, thus suggesting a contribution of NALCN to LC NAN firing. We also tested the effects of the NALCN channel inhibitor, L-703-606, as well as neurotensin and substance P which activate NALCN through G-protein coupled receptors. We found that L-703-606 decreased firing while neurotensin and substance P increased firing in a subset of LC NANs. We are currently testing mice in which NALCN has been deleted in dopamine-β-hydroxylase (DBH)-expressing neurons. In behavioral experiments, we are testing the effect of NALCN deletion in the LC on sleep and attention. In future experiments, we will examine NALCN's role in Gq-coupled receptor-mediated activation of LC neurons projecting to different regions involved in PD symptoms, and we will conduct further whole-cell patch-clamp electrophysiological experiments in the NALCN $^{fl/fl}$ - DBH-Cre ^{het} mouse line to understand how NALCN channels within the LC affect the NANs' action potential characteristics. Illuminating NALCN's role in LC firing may inform future investigations that focus on understanding the loss of LC neurons' role in PD and DA-releasing neuron degeneration.

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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

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Program #/Poster #: PSTR045.16/O8

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

Support: R01AG069196
R01AG074216
R01AG077541

Title: Cellular, Synaptic and Network Signatures of Aging in the Olfactory Bulb

Authors: *C. UZUN[1], D. ZHAO[2], M. HU[2], Z. QIAO[2], Y. LI[2], S. LIU[2];
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Abstract: Olfactory dysfunction is a common feature of aging and an early hallmark of neurodegenerative diseases, including Alzheimer's and Parkinson's disease. These disorders show strong age- and sex-related differences in prevalence, understanding how aging and sex influence olfactory processing is critical. However, the cellular and synaptic mechanisms underlying age- and sex-dependent olfactory dysfunction remain poorly understood.Olfactory epithelium receptor neurons in the epithelium project directly onto mitral cells in the olfactory bulb (OB), which in turn send long-range axons to the entorhinal cortex, piriform cortex, and other limbic regions. Given their extensive connectivity, these projection neurons may be particularly vulnerable to age- and sex-dependent alterations.To test this hypothesis, we assessed odor detection performance in young adult and aged C57BL/6J mice of both sexes and found that aged mice exhibited reduced sensitivity to food odors compared to their young counterparts. Consistently, our in vivo electrophysiological studies with high-density multi-channel probes from awake but head-fixed mice demonstrated age-dependent reduction in neuronal excitability and alterations in network oscillatory activity within the mitral cell layer. At the cellular level, whole-cell patch-clamp recordings in OB slices revealed a depolarized membrane potential in aged male mice, while increased membrane resistance was observed in both aged males and females. Consistently, mitral cells from aged mice exhibited elevated spontaneous firing rates and reduced afterhyperpolarization. These in vitro eletrophysiological studies further identified significant age-dependent alterations in multiple parameters of spontaneous and evoked action potentials, including threshold, frequency, and amplitude, collectively indicating enhanced intrinsic excitability in aged MCs. The discrepancy between in vivo and in vitro electrophysiological findings suggests a role of network or synaptic dysfunction. Align to this prediction, our work a the synaptic level further revealed a significant and age-dependent reduction of spontaneous excitatory synaptic activities in the mitral cells. Taken together, these findings demonstrate that aging reshapes the functional dynamics and connectivity of the OB circuits, leading to impaired odor processing and detection. This study provides new insights into the cellular, synaptic, and network mechanisms
underlying age-related olfactory decline and identifies potential early biomarkers of brain aging and neurodegenerative disease with olfactory dysfunction as early symptoms.

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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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

Support: NIDCD T32 - DC005361
NIHP51OD010425
NS123959
Virginia Merrill Bloedel Trainee Award

Title: Regional specializations in the intrinsic biophysical properties of supragranular pyramidal neurons in primate temporal cortex

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Abstract: The primate cerebral cortex exhibits a remarkable expansion of glutamatergic neuron types relative to rodents. Among these, layer 5/6 infragranular neurons have been well characterized by their distinct morpho-electric properties across various neocortical regions. However, the extent to which regional specializations exist in the supragranular (layer 2/3) layers remains unclear. A recent study identified an enrichment of Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) channel expression in layer 2/3 neurons of the temporal cortex, raising the possibility that supragranular neurons can likewise be classified into distinct types based on their intrinsic firing properties. Building on the known cellular diversity of the macaque temporal cortex, we sought to characterize cell-type-specific regional specializations of excitatory neurons within this area. Here we present data profiling distinct excitatory neuron types across primary auditory and association regions of the macaque temporal cortex.To establish regional specializations within the temporal cortex at the cellular level, we performed patch-seq recordings from individual neurons in quiescent ex vivo slices pharmacologically isolated using synaptic blockers. Neocortical tissue was collected from primary auditory cortex (core regions) and auditory association cortex of *M.* Nemestrina (n = 10 female; n = 2 male), *M. Fascicularis* (n = 3 male; n = 3 female), and *M.* Mulatta (n = 1 female; n = 2 male) macaques. Animal subjects ranged in age from 3-22 years old (mean age: 10.2 ± 1.6 years). The biophysical properties of neurons were collected using intracellular patch-clamp recordings from both acute and cultured *ex vivo* brain slices at a temperature of 30-32°C. Data was collected from a total of 138 neurons (n = 45 caudal auditory core, n = 54 rostral auditory core, n = 39 auditory association cortex). Electrophysiological recordings reveal that supragranular neurons located in the caudal areas of primary auditory cortex exhibit higher input resistance, higher firing rates, and action potentials with a shorter half-width compared to neurons in auditory association cortex. Supragranular neurons in the primary auditory cortex also displayed more pronounced HCN-dependent membrane properties compared to neurons in auditory association cortex. As in other brain regions, neurons across different regions of the macaque temporal cortex can be distinguished

based on several electrophysiological signatures. Collectively these findings suggest that different topographic regions of the primate temporal cortex are specialized at the level of individual neurons' intrinsic properties.

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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.18/P2

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

Support: NIH Grant 5R01MH138515-02

Title: Electrophysiological characterization of neurons in the Supramammillary Nucleus of the Hypothalamus

Authors: *W. FRANCESCONI[1], B. THADARI[1], F. BERTON[2], J. A. DABROWSKA[3]; [1]Rosalind Franklin Univ. of Med. and Scien, North Chicago, IL; [2]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ., North Chicago, IL; [3]Chicago Med. Sch. RFUMS, North Chicago, IL

Abstract: The Supramammillary nucleus (SuM) is a heterogeneous hypothalamic structure involved in hippocampal theta regulation, arousal, locomotion, motivational states, and social recognition memory. Although anatomical and molecular diversity within the SuM has been described, the intrinsic electrophysiological mechanisms governing SuM neuronal excitability remain unknown. Here, we electrophysiologically characterized the intrinsic firing properties of SuM neurons from both male and female adult Sprague-Dawley rats in the presence of synaptic blockers. We used whole-cell current-clamp recordings from SuM neurons in acute brain slices, and applied 1000 ms depolarizing current pulses normalized to rheobase. We quantified the firing output of these neurons by gain (Hz/pA), defined as the slope of firing frequency above the rheobase and maximum firing output (Hz). To understand how neuronal firing adapts to sustained depolarizing input, we also measured adaptation index defined as the ratio of firing in the last 300ms to firing in the first 300ms. Analysis of firing patterns revealed two types: early-inactivating neurons that fired transiently within the first 200-300 ms, and persistent-firing neurons that fired throughout the 1000 ms pulse. Adaptation index correlated significantly with gain ($r = 0.39$, $p = 0.008$, $n = 46$) and maximum firing rate ($r = 0.45$, $p = 0.002$, $n = 46$), indicating that persistent-firing neurons have higher excitability than early-inactivating neurons. These findings reveal that SuM neurons may have electrophysiologically distinct subpopulations that differ in their excitability, providing a framework for understanding how SuM neurons could differentially encode or transmit information under diverse behavioral contexts.

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Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

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Program #/Poster #: PSTR045.19/P3

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

Support: ERC grants, SYNEME: 742106, HYPOMETAB: 101142538
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Title: Mitochondrial fission factor controls mitochondrial Ca^{2+} handling and neuronal activity in AgRP neurons

Authors: *G. YEGHIAZARYAN[1], H. FENSELAU[2], P. KLOPPENBURG[1];
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Abstract: Orexigenic AgRP neurons of the arcuate nucleus of the hypothalamus are critical regulators of energy and glucose homeostasis. Their activity is influenced by dynamic adaptations of the mitochondrial network through cycles of fusion and fission. Mitochondrial fission factor (MFF), an outer mitochondrial membrane protein, promotes mitochondrial fragmentation by recruiting the core fission machinery. To investigate the role of MFF in AgRP neurons, we generated AgRP-specific MFF knockout mice and assessed mitochondrial morphology, function, neuronal activity, and feeding behavior. Loss of MFF increased mitochondrial size in both AgRP neuron somata and PVN-projecting axons. The enlarged mitochondria exhibited enhanced Ca^{2+} uptake capacity, increased mitochondrial membrane potential, and a more reduced NAD(P)H redox state, indicating altered mitochondrial bioenergetics. Patch-clamp recordings revealed increased excitability of MFF-deficient AgRP neurons, particularly under conditions associated with elevated intracellular Ca^{2+} loads. Enhanced mitochondrial Ca^{2+} buffering is expected to reduce calcium-dependent hyperpolarizing currents, thereby limiting spike-frequency adaptation and promoting sustained neuronal firing. At the synaptic level, MFF deficiency altered neurotransmission, resulting in increased asynchronous neurotransmitter release following high-frequency stimulation. At the behavioral level, mice lacking MFF in AgRP neurons exhibited enhanced food intake during energy-state transitions, consistent with increased AgRP neuron output. Together, these findings identify MFF-dependent mitochondrial fission as a key regulator of mitochondrial Ca^{2+} homeostasis, neuronal excitability, synaptic function, and feeding behavior. The results establish a mechanistic link between mitochondrial dynamics and hypothalamic circuit function, highlighting how cell-

type-specific regulation of mitochondrial architecture contributes to the control of systemic metabolism.

Disclosures: G. Yeghiazaryan: None. **H. Fenselau:** None. **P. Kloppenburg:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.20/P4

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

Support: NIH/NINDS R01-NS110575
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Title: Concurrent changes to the AIS and dendritic field help to maintain consistent intrinsic sensitivity in RGCs during retinal degeneration

Authors: *S. FRIED[1,2], M. YUNZAB[1], F. M. NADAL-NICOLAS[3], S. F. STASHEFF[4], P. WERGINZ[5];
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Abstract: The size and location of the axon initial segment (AIS) varies for different types of retinal ganglion cells (RGCs), contributing to differences in intrinsic sensitivity across types. AIS differences are also thought to confer differences in response sensitivity to the artificial stimulation used by retinal implants. AIS properties are altered in response to disease in many other types of (non-retinal) CNS neurons, suggesting they might be altered similarly in the degenerating retina. Understanding such differences is critical to developing effective implants or other treatments for retinal disease. Here, we compared AIS properties in ON alpha sustained (ON-αS) RGCs of the healthy retina (*wt*) to those in age-matched mice with retinal degeneration (*rd10*); measurements were repeated at post-natal days 15, 30, 90, and 200 (P15-200), allowing the full developmental trajectory to be captured in both healthy and diseased cells. We also analyzed the detailed morphology of all cells from which AIS measurements were made, as well as physiological sensitivity in a subset of adult cohorts. AIS lengths were reduced in *rd10* mice, often as early as P30, and remained shorter for all subsequent timepoints. Somatodendritic

measurements revealed a concurrent decrease in dendritic field size. Somewhat surprisingly, however, there was little difference in physiological sensitivity between healthy and diseased cells, in contrast to what occurs in many other CNS neurons when AIS properties are altered. Computational modeling revealed that while the shortening of the AIS indeed reduces sensitivity in RGCs, the concurrent reduction of somatodendritic size effects an opposing increase in sensitivity. Thus, our results indicate a form of homeostasis in which changes to multiple structural components combine to maintain intrinsic sensitivity at levels similar to that of *wt* RGCs. This homeostatic response stands in stark contrast to that reported in other CNS neurons in which AIS changes are not accompanied by changes in somatodendritic size, and thus, intrinsic sensitivity is altered between *wt* and diseased cells. It will be interesting in future studies to learn how and why nature chooses between these different options.

Disclosures: S. Fried: None. **M. Yunzab:** None. **F.M. Nadal-Nicolas:** None. **S.F. Stasheff:** None. **P. Werginz:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.21/P5

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

Support: NIH Grant R00NS121399
Esther A. & Joseph 561 Klingenstein Fund
Vanderbilt School of Medicine Dean's Office
NIH Grant T32GM137793

Title: Distinct electrophysiological signatures reveal neuronal heterogeneity in the mouse fasciola cinereum

Authors: S. INCONTRO, L. GUO, M. DRYDEN, C. CLARK, ***Q. NGUYEN**;
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Abstract: The fasciola cinereum (FC) is a small, conserved hippocampal subregion whose cellular properties remain poorly understood. Anatomically positioned between dorsal CA1 and the third ventricle, the FC receives diverse cortical and subcortical inputs but is often excluded from hippocampal circuit models. Here, we performed ex vivo whole-cell patch-clamp recordings in mouse hippocampal slices to define the intrinsic and synaptic properties of FC neurons. We find that FC neurons are electrophysiologically and morphologically distinct from neighboring CA1 and CA2 pyramidal cells, exhibiting reduced intrinsic excitability, delayed spike initiation, and enhanced afterhyperpolarizations. These properties are strongly shaped by potassium conductances, with Kv2 (KCNB) and Kv7 (KCNQ) channels contributing to the suppression of firing. We find that FC neurons span a continuum of intrinsic excitability which is

structured by variability in potassium channel-mediated conductances and is inversely coordinated with excitatory synaptic input, such that less excitable neurons receive stronger synaptic drive. Together, these findings establish a mechanistic framework in which intrinsic membrane properties and synaptic input are co-organized across the FC population, providing new insight into how this understudied hippocampal region may contribute to the regulation of neural excitability.

Disclosures: S. Incontro: None. **L. Guo:** None. **M. Dryden:** None. **C. Clark:** None. **Q. Nguyen:** None.

Poster

PSTR045: Intrinsic Excitability: Cell Types, Regional Specialization, and Disease-Related Remodeling

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR045.22/P6

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

Support: KAKENHI 24H02336, 25K09842

Title: Modeling analysis of the energy efficiency of retroaxonal action potentials propagating along hippocampal mossy fibers

Authors: *H. KAMIYA[1], S. OHURA[2];
[1]Neurobio., Hokkaido Univ. Grad. Sch. of Med., Sapporo, Japan; [2]Neurobio., Hokkaido Univ. Grad. Sch. of Med., Sapporo-shi, Japan

Abstract: Axonal spikes are reliable neuronal codes propagating from the initiation site located on the proximal axon, usually at the axon initial segments, toward the presynaptic terminals on the distal axon. In addition to this conventional orthodromic propagation, it has been suggested that a non-canonical mode called retroaxonal action potentials is triggered from distal axons in some experimental conditions. We previously reported that robust afterdischarges, consisting of bursts of retroaxonal action potentials, are generated by applying strong repetitive stimuli to the hippocampal mossy fiber model in conjunction with small depolarization of distal axons. To better characterize the properties of this non-canonical axon signaling, this study aimed to compare the energy demand of orthodromic and retroaxonal action potentials with computer simulation using the mossy fiber model. Since K^+ efflux electrically counteracts Na^+ influx and thereby causes the waste of energy to re-establish the electrochemical gradient through energy-consuming ion pumps. Therefore, the energy consumption by axonal action potentials can be evaluated by quantifying the temporal overlap of Na^+ and K^+ currents. As in the previous experimental study, it was demonstrated that axonal action potentials in the hippocampal mossy fiber model were generated highly efficiently with a small overlap of Na^+ inflow and the delayed K^+ outflow, thereby saving the energy demand of axonal spikes. Intriguingly, the overlaps of the Na^+ and K^+ currents during retroaxonal action potentials, induced by repetitive stimulation in

conjunction with small depolarization of distal axons, were much smaller than those of orthodromic action potentials. These results suggested that retroaxonal action potentials during afterdisharges carry neuronal information more efficiently in terms of energy consumption. This mechanism may compensate for the energy demand of strong burst activity during afterdischarges.

Disclosures: H. Kamiya: None. **S. Ohura:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.01/Q1

Topic: B.09. Glial Mechanisms

Support: Grant-in-Aid for Scientific Research (C) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) in Japan (20K07756, 24K10486)(N.S.)
Fund for the Promotion of Joint International Research (Fostering Joint International Research (B)) of the MEXT in Japan (20KK0188)(N.S.)
research grant for basic sciences from Sumitomo Foundation (200490) (N.S.)

Title: The molecular function of 14-3-3s in survival of dysmyelinated small-diameter axons in the CNS

Authors: *N. YAMADA[1], H. SAITO[1,2,3], R. TAKAHASHI[2], M. FUJISATO[1], B. SASAKI[1], M. YAMADA[2], S. ABE[1], A. YOSHIMOTO[1], R. OHKAWA[1], M. SIMONS[4,5], N. SUZUKI[1,2]; [1]Grad. Sch. of Med. and Dent. Sciences, Inst. of Sci. Tokyo, Bunkyo-ku/Tokyo, Japan; [2]Grad. Sch. of Med. and Dent. Sciences, TMDU, Bunkyo-ku/Tokyo, Japan; [3]Div. of Surgical Pathology, Inst. of Sci. Tokyo Hosp., Bunkyo-ku/Tokyo, Japan; [4]Inst. of Neuronal Cell Biology, Tech. Univ. Munich, Munich, Germany; [5]German Ctr. for Neurodegenerative Dis., Munich, Germany

Abstract: In the CNS, oligodendrocyte (OL) form myelin around nerve axons, which enables efficient conduction of action potentials and maintains axonal homeostasis. Therefore, in demyelinating diseases such as multiple sclerosis, small-diameter (SD) axons in particular degenerate and eventually disappear. Teneurin-4, a neuronal and OL transmembrane protein, deficient mice (Ten-4 -/- mice) exhibit dysmyelination of SD axons, but survive for more than one year. In this study, we aimed to elucidate the molecular mechanisms of survival of SD axons without myelin using Ten-4 -/- mice. First, we performed immunohistochemistry (IHC) of neurofilament (NF) in the dorsal column of the spinal cord in Ten-4 -/- mice. As a result, abnormally diffused and strong staining of NF was observed. Moreover, the expression of dephosphorylated NF, a marker of axonal degeneration, was higher in Ten-4 -/- mice, compared with wild-type mice. Next, electron microscopy (EM) analysis unexpectedly revealed that SD axons in Ten-4 -/- mice survived at the age of 1 year, despite the loss of myelin, axonal cytoskeleton collapse and mitochondrial hypertrophy. To clarify the molecular mechanisms of

the survival of dysmyelinated axons, we performed a proteomics analysis of the Ten-4 -/- tissue by mass spectrometry. The results showed increases in axonal cytoskeletal proteins and mitochondrial-related proteins, consistent with the results of IHC and EM analyses. Interestingly, four of the seven 14-3-3 isoforms were highly expressed in the Ten-4 -/- SD axons and additional IHC analysis revealed that the 14-3-3 protein is specifically expressed in Ten-4 -/- SD axons but not in astroglia or microglia. These results suggest that 14-3-3s are the potent regulator of the survival of dysmyelinated SD axons. Finally, we performed inhibition experiments of the 14-3-3s function in Ten-4 -/- mice. EM analysis showed that 14-3-3s inhibition by an administration of BV02, a chemical inhibitor of 14-3-3, significantly reduced the size of microtubules and mitochondria, suggesting the progression of axonal degeneration. To analyze a more specific inhibitory effect, we injected the AAV-PHP.S that expresses difopein, an artificial peptide inhibitor of 14-3-3, which was driven under the synapsin-1 promoter, into Ten-4 -/- mice. A similar result was obtained as in the inhibition experiment using BV02. In summary, 14-3-3s are revealed to be an important factor for the survival of dysmyelinated SD axons. Our findings are expected to elucidate the pathology of demyelinating diseases, the associated axonal degeneration, and the development of new treatments.

Disclosures: N. Yamada: None. **H. Saito:** None. **R. Takahashi:** None. **M. Fujisato:** None. **B. Sasaki:** None. **M. Yamada:** None. **S. Abe:** None. **A. Yoshimoto:** None. **R. Ohkawa:** None. **M. Simons:** None. **N. Suzuki:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.02/Q2

Topic: B.09. Glial Mechanisms

Support: Project 400005 (Institutional Commitment AA)

Title: Toward in vivo gene-editing therapy for Pelizaeus-Merzbacher disease: selective OPC expansion in a conditional Plp1 G74E mouse model

Authors: *X. TAO[1], C. ZHAO[2], D. LIU[3], F. URNOV[4], M. CHAVALI[5], D. H. ROWITCH[1]; [1]Guerin Children's, Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]Wellcome-MRC Cambridge Stem Cell Inst., Univ. Cambridge, Cambridge, United Kingdom; [3]Broad Institute/Harvard University/HHMI, Cambridge, MA; [4]Innovative Genomics Inst., Berkeley, CA; [5]Pediatrics/Neuroscience, Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Pelizaeus-Merzbacher disease (PMD) is an X-linked congenital leukodystrophy caused by mutations in *PLP1*, with no effective disease-modifying treatment. Because oligodendrocyte precursor cells (OPCs) persist and proliferate throughout life, they may provide a self-renewing target population for therapeutic gene correction. Here, we generated a clinically relevant conditional knock-in mouse model carrying the *Plp1* G74E mutation (*Plp1^iG74E*), in

which mutant allele expression is Cre-dependent. Activation of mutant *Plp1* in the oligodendrocyte lineage using Sox10-Cre caused reduced survival, impaired motor function, and severe hypomyelination compared with control littermates. RNAscope and immunohistochemical analyses revealed a marked loss of mature oligodendrocytes in PMD mice, accompanied by increased expression of cellular stress markers including CHOP and ATF4. Notably, oligodendrocyte-lineage cells that escaped Cre-mediated recombination expanded over time, suggesting positive selection for cells without mutant Plp1 expression. Because the short lifespan of the full oligodendrocyte-lineage PMD model limits long-term therapeutic testing, we generated a regional PMD model by crossing *Plp1^iG74E* mice with Emx1-Cre, restricting mutant allele expression to cortical and hippocampal regions. Developmental immunohistochemical analysis showed severe depletion of oligodendrocyte-lineage cells in targeted regions. Together, these findings establish a conditional PMD mouse model that recapitulates key pathological features of leukodystrophy and reveals selective expansion of non-recombined OPCs. This selective advantage provides a rationale for therapeutic gene correction, where even inefficient editing may be amplified by expansion of corrected OPCs. We are therefore combining the regional PMD model with the SELECTIV platform to enable target-cell expression of Cas9 and AAV receptors, followed by AAV delivery of sgRNA and single-stranded DNA donor templates for homology-directed repair of the mutant allele. This approach will test whether genetically corrected OPCs can repopulate diseased tissue and support myelin repair.

Disclosures: X. Tao: None. **C. Zhao:** None. **D. Liu:** None. **F. Urnov:** None. **M. Chavali:** None. **D.H. Rowitch:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR046.03/Q3

Topic: B.09. Glial Mechanisms

Support: the Grant-in-Aid for Scientific Research (C) of the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) in Japan (24K10486)
the research grant from Japan Agency for Medical Research and Development (AMED) (JP26gk0210041)

Title: Oligodendrocyte Lineage Cell Responses to Stress- and Inflammatory-induced Factors

Authors: *S. ABE[1], H. MISAWA[1], B. SASAKI[1], N. YAMADA[1], M. FUJII[2], N. SUZUKI[1]; [1]Grad. Sch. of Med. and Dent. Sciences, Inst. of Sci. Tokyo, Bunkyo-ku/Tokyo, Japan; [2]Inst. of Sci. Tokyo, Bunkyo-ku/Tokyo, Japan

Abstract: Oligodendrocytes (OLs) play an essential role in the CNS by producing myelin sheaths that support rapid impulse propagation along the axon. Accumulating evidence suggests

that OL dysfunction and demyelination contribute not only to demyelinating diseases such as multiple sclerosis (MS) but also to the pathophysiology of neurodegenerative and psychiatric disorders, including Alzheimer's disease (AD) and depression. Elevated levels of inflammatory cytokines and stress-related factors, including IL-1β, TNF-α, IL-6, glucocorticoids (GCs), and glutamate (Glu), have been reported in lesions from these disorders. OLs and their precursor cells (OPCs), express receptors for these factors, as do other glial cell types. However, the mechanisms underlying their responses to these stimuli remain poorly understood. Therefore, to investigate the direct effects of these factors on the differentiation and survival of OLs and OPCs, we performed the following experiments. Primary cultures of OPCs were prepared from the cerebral cortices of rat pups. To investigate the effects of inflammatory cytokines and stress-related factors on OL differentiation, IL-1β, TNF-α, IL-6, Glu, or GC were added to the culture medium during the induction of OPC differentiation into OLs. As a result, we found that when these factors were included, cells with longer, thicker processes but fewer branches than normal OLs were more often observed than in controls. Immunocytochemistry showed that these cells were positive for GFAP, an astrocyte marker. Furthermore, we observed multiple cells that exhibited OL-like morphology and expressed GFAP while still retaining the expression of OL markers. Based on their morphology and immunostaining results, it was possible that they acquired the astrocytic character through differentiation from OPCs or conversion from OLs in the culture condition. These results suggest that the aberrant differentiation/conversion of OL lineage cells is induced by the inflammatory and stress-induced factors. We also found that the expression of Sgk1, which activates STAT3, an upstream regulator of the GFAP gene transcription, was upregulated in the presence of GC. Furthermore, we observed some differences in the differentiation/conversion and survival of these cells between female and male OLs, implying that it may be related to the sex differences in MS, AD, and depression. Our findings should be useful for a better understanding of the role of OL lineage cells in the pathogenesis of the diseases.

Disclosures: S. Abe: None. **H. Misawa:** None. **B. Sasaki:** None. **N. Yamada:** None. **M. Fujii:** None. **N. Suzuki:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.04/Q4

Topic: B.09. Glial Mechanisms

Title: A Bipolar Patient-Derived Pipeline from Fibroblast Metabolism to Oligodendrocyte Phenotyping

Authors: *A. K. LINDEN, B. THROESCH, B. BALANA, P. BONAVENTURE; Neurosci., Johnson&Johnson, San Diego, CA

Abstract: Myelination is an active and dynamic process fundamental to neural circuit formation and the fine-tuning of neuronal signaling. Myelin, a lipid rich insulation for neurons, is generated by mature oligodendrocytes within the central nervous system. Convergent evidence from postmortem, genetic, imaging, and molecular studies implicates oligodendrocyte dysfunction in Bipolar Disorder (BD). For example, evidence of reduced oligodendrocyte density in white matter and downregulation of canonical maturation and myelin genes such as MBP, PLP1, MAG, and MOG suggests impaired myelination in BD patients. In addition, BD cohorts frequently show signatures of mitochondrial dysregulation including reduced electron-transport chain subunit expression, decreased oxidative phosphorylation, and a compensatory shift toward glycolytic metabolism. This bioenergetic reprogramming can limit ATP availability, thereby constraining lipid precursor supply and membrane assembly essential for myelin production and sheath compaction.
Because *in vivo* correlates of cellular phenotypes are limited, we developed an *in vitro* platform to determine disease-associated phenotypes within BD versus healthy patients. Fibroblasts from healthy and BD patients were purchased from Coriell Institute of Medical Research and were assessed for a bioenergetic phenotype using a seahorse mitochondrial stress test. BD fibroblasts exhibited a reduction in mitochondrial respiration at baseline and maximal respiration conditions compared to healthy fibroblasts, indicative of bioenergetic dysregulation. Fibroblasts then underwent reprogramming into iPSCs and colonies with stereotypical morphological properties were selected for expansion and additional testing. Validation of successful iPSC generation was conducted using RNA expression for pluripotency vs fibroblast markers, immunocytochemistry for pluripotency gene expression, and genomic DNA assessment for chromosomal abnormalities, and three clones per patient were selected for karyotyping to ensure proper chromosomal structure. This validated platform may be used to assess BD disease-associated oligodendrocyte maturation and myelination phenotypes.

Disclosures: A.K. Linden: A. Employment/Salary (full or part-time):; Johnson & Johnson. **B. Throesch:** A. Employment/Salary (full or part-time):; Johnson&Johnson. **B. Balana:** A. Employment/Salary (full or part-time):; Johnson&Johnson. **P. Bonaventure:** A. Employment/Salary (full or part-time):; Johnson&Johnson.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.05/Q5

Topic: B.09. Glial Mechanisms

Title: A xeno-free, human iPSC-derived in vitro model of OPCs and oligodendrocytes for studying demyelinating diseases

Authors: H. GARNETT[1], A. VETELEANU[1], N. JAMES[2], T. TATAR OZKAN[1], **J. FAIRCHILD**[1], *A. BYRNE[1], S. HUSSAIN[1], S. MILDE[1], C. ARUTHAN[1], J. HUNDLING[1], V. YIANNI[1], B. NEWMAN[1], K. FIRTH[1], G. MASTROGIOVANNI[1], T. OOSTERVEEN[3], W.

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Abstract: Oligodendrocyte precursor cells (OPCs) are proliferative progenitor cells that generate myelinating oligodendrocytes (OLs) during CNS development and in response to injury. Pathological features of demyelinating diseases, such as multiple sclerosis, include impaired OPC differentiation, OL loss, and disrupted myelination. Human in vitro models of OLs and OPCs are lengthy and complex to generate, thus limiting widespread adoption and resulting in researchers relying on rodent models. Furthermore, typical iPSC-derived OL culture requires the use of animal-derived components, which can affect reproducibility, translational impact, and predictive accuracy when mimicking human biology. As such, optimising cell culture protocols for xeno-free reagents is important to provide robust and reproducible data. Here, we describe the generation of human iPSC-derived oligodendroglial cells (ioOligodendrocyte-like cells, ioOLCs) and oligodendrocyte precursor cells (ioOPC-like cells, ioOPCs) using our opti-ox™ deterministic cell programming technology. Post-thaw, the ioOLCs exhibit an OPC-like morphology on day 1 and express the oligodendroglial marker O4. By day 8, the cells acquire an OL-like morphology and upregulate maturation markers, including MBP, as demonstrated by bulk RNA-seq and scRNA-seq. In co-culture with ioGlutamatergic Neurons, ioOLCs demonstrate enhanced MBP expression, showcasing their utility for axon-glia interaction studies. We have demonstrated that the ioOPCs have the capacity to proliferate for up to 14 days and express OPC markers, including PDGFRA. Upon switching to maturation medium, the cells downregulate PDGFRA, upregulate MBP and other mature markers, and acquire an oligodendrocyte-like morphology. To assess the suitability of xeno-free reagents for ioOLC and ioOPC cell culture, we systematically tested the coating matrices including Laminin-521, and Laminin-221, the dissociation reagent TrypLE, small molecules and human serum albumin in the cell culture media. Performance was benchmarked against their animal-derived counterparts to confirm the appropriate cell morphology and minimal change in key markers, as assessed by immunocytochemistry and qPCR. Ongoing results suggest that Laminin-521 is comparable to the animal-derived Laminin based on cell culture morphology and consistency. Our ioOLCs and ioOPCs provide human-relevant, consistent in vitro models to study the role of these cells in disease mechanisms, and support the development of novel therapeutics for neurodegenerative and demyelinating diseases.

Disclosures: H. Garnett: A. Employment/Salary (full or part-time):; bit.bio. **A. Veteleanu:** A. Employment/Salary (full or part-time):; bit.bio. **N. James:** A. Employment/Salary (full or part-time):; bit.bio. **T. Tatar Ozkan:** A. Employment/Salary (full or part-time):; bit.bio. **J. Fairchild:** A. Employment/Salary (full or part-time):; bit.bio. **A. Byrne:** A. Employment/Salary (full or part-time):; bit.bio. **S. Hussain:** A. Employment/Salary (full or part-time):; bit.bio. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio. **C. Aruthan:** A. Employment/Salary (full or part-time):; bit.bio. **J. Hundling:** A. Employment/Salary (full or part-time):; bit.bio. **V. Yianni:** A. Employment/Salary (full or part-time):; bit.bio. **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio. **K. Firth:** A. Employment/Salary (full or part-time):; bit.bio. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time):; bit.bio. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.06/Q6

Topic: B.09. Glial Mechanisms

Support: NIA/NIH R01AG078565

Title: The GP130/STAT3 pathway is a common signaling cascade activated in oligodendrocytes in neurodegenerative diseases

Authors: *V. BUI[1,2], J. COAKLEY[1], G. THOMAS[3], S. H. KANG[4];
[1]Temple Univ., Philadelphia, PA; [2]Dept. of Neural Sci., Ctr. for Neural Develop. and Repair, Philadelphia, PA; [3]Shriners Pediatric Res. Ctr., Temple Univ. Med. Sch., Philadelphia, PA; [4]Neural Sci., Temple Univ. Sch. of Med., Philadelphia, MD

Abstract: CNS glial cells respond to injury or disease by changing their morphology, gene expression, and cellular activities. These collective responses, known as glial reactivity, significantly affect the course of cellular degeneration or the repair process of neighboring neurons and other glial cells following injury. While the reactive responses of astrocytes, microglia, and oligodendrocyte precursor cells (OPCs) are well documented, the responses of oligodendrocytes (OLs) remain underexplored.
To investigate oligodendroglial reactivity in diseases, we performed OL-specific RNA sequencing on the translating mRNAs from OLs in 14-month-old APP/PS1 mice and their age-matched healthy controls. Our results revealed that signal transducer and activator of transcription 3 (STAT3) was among the significantly upregulated genes in OLs. Consistent with this, we confirmed an increase in phospho-STAT3 (p-STAT3) immunoreactivity in OLs as well as in astrocytes near amyloid plaques. We also observed elevated P-STAT3 signals in OLs within the spinal cords during advanced stages of the disease in SOD1 (G93A) mice. Increased p-STAT3 signals were also found near injury sites in rodent models of contusive spinal cord injury (SCI) and traumatic brain injury (TBI).
To identify upstream membrane receptors that mediate extracellular signaling to STAT3 activation in OLs, we crossed *Il6st*-floxed mice with OL-specific Cre and APP/PS1 or SOD1 (G93A) mice. This process selectively deletes GP130, a common subunit for the IL-6 receptor family, from OLs, resulting in almost all p-STAT3 signals in OLs being abolished in those diseased mice and those affected by TBI. This indicates that GP130 is required for STAT3 activation in OLs. Interestingly, when STAT3 signaling was disrupted by deleting GP130 or STAT3 from OLs, the patterns of astroglial p-STAT3 were altered.
Our results suggest that the GP130/STAT3 pathway is a common signaling cascade activated in OLs in response to neuroinflammation across various neurodegenerative diseases and injuries. In addition, there may be signaling crosstalk between OLs and astrocytes via STAT3 downstream players.

Disclosures: V. Bui: None. **J. Coakley:** None. **G. Thomas:** None. **S.H. Kang:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.07/R1

Topic: B.09. Glial Mechanisms

Title: Loss of Oligodendrocyte Maturation Factor Leads to Severe White Matter Degeneration in Mouse Anterior Commissure

Authors: *K. PHAN[1], Y. LIU[1], D. M. SHERRY[2], A. C. JOHNSON[3], I. DUNN[1];
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Abstract: The Oligodendrocyte Maturation Factor (OMF) gene is located on mouse chromosome 17. A mutational analysis identified a 59-base pair long deletion that occurred in the first intron of the OMF gene that caused developmental neurological abnormalities. Homozygous OMF^{null} mice were born healthy and appeared anatomically normal up to two weeks of age. However, after postnatal day 14 (P14), they were smaller than normal, exhibited ataxic gait, became lethargic, and died shortly after postnatal day 24 (P24). Transcriptome analysis at P14 and P23 revealed significantly reduced expression of mitochondrial genes in OMF^{null} brains compared to wild-type controls, including mt-Nd4, mt-Cytb, mt-Nd2, mt-Co1, mt-Atp6, and others. Similarly, genes specific for myelinating oligodendrocytes also showed reduced expression in P23 OMF^{null} brains compared to controls. As such, our hypothesis is that loss of OMF reduces mitochondrial energy metabolism, which disrupts oligodendrocyte maturation, leading to impaired myelination and neurological abnormalities. Immunohistochemistry analysis revealed a significant reduction in OLIG2-positive cells (developing oligodendrocytes) and CC1-positive cells (mature oligodendrocytes) in OMF^{null} mice. Examination in the anterior commissure of OMF:CNP:EGFP mice demonstrated significantly impaired myelination and widespread vacuolation. Vascular integrity in the anterior commissure was also compromised, as evidenced by a decrease in CD31 (vascular endothelial cells) expression. Neurofilament heavy chain (NF-H) staining in OMF^{null} anterior commissure revealed less organized NF-H-positive axon bundles. Examination of nodes of Ranvier demonstrated a reduced number and shortened spacing, indicating that OMF deletion disrupts nodes. At the ultrastructural level, OMF-deficient animals demonstrated myelin decompaction, which confirmed severe defects in myelin sheath structure. Together, these findings identify OMF as a critical factor for oligodendrocyte maturation, myelin stability, and nodal organization, while also implicating OMF as necessary for mitochondrial function in early development. Understanding OMF's role may reveal new insights into the molecular mechanisms underlying myelin-related disorders and highlights potential therapeutic options targeting myelin integrity.

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Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

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Program #/Poster #: PSTR046.08/R2

Topic: B.09. Glial Mechanisms

Support: NINDS (DP2NS148743)

Title: In vivo screen of repurposed therapeutics for preterm white matter injury

Authors: *L. ODELL[1], S. PANIGRAHI[1], J. R. CHAN[2], B. E. OSTREM[3];
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Abstract: Introduction: Preterm White Matter Injury (WMI) is the most common form of brain injury in preterm neonates. WMI involves an arrest of differentiation of oligodendrocytes (OLs), the myelinating cells of the central nervous system, leading to hypomyelination and subsequent long-term cognitive and motor neurodevelopmental impairment. Current treatment options for WMI are limited to symptom management, with no existing therapies that target the underlying mechanism of the injury. A prior *in vitro* screen of FDA-approved medications identified two compounds, phenytoin and oxybutynin, that promote OL differentiation and myelination. Phenytoin is an antiseizure medication commonly administered to treat acute seizures in preterm infants, and oxybutynin is occasionally prescribed to infants with posterior urethral valves to manage bladder dysfunction. We aimed to validate these promyelinating effects in an in vivo mouse model of WMI.
Methods: In this mouse model of WMI, neonatal mice are dosed with test compounds or vehicle solution via oral gavage once daily while being exposed to 10% FiO_2 from postnatal day 3 (P3) through P10. Mouse brain development and developmental myelination from P3 to P10 mirrors human brain development from gestational weeks 23 through 40, and exposure to hypoxia during this time allows for a recapitulation of the typical WMI phenotype. We assessed oligodendrocyte differentiation and density and myelin intensity at P10 by immunohistochemistry in the brain after treatment with oxybutynin, phenytoin or vehicle.
Results: There was a significant increase in the proportion of mature OLs between vehicle animals and both phenytoin-treated animals *($p=0.002$, one-way ANOVA followed by post hoc Dunnett's test)* and oxybutynin-treated animals *($p=0.004$, one-way ANOVA followed by post hoc Dunnet's test)* in the cortex. There was also a statistically significant increase in myelin basic protein (MBP) intensity between vehicle animals and both phenytoin-treated animals *($p<0.001$, one-way ANOVA followed by post hoc Dunnett's test)* and oxybutynin-treated animals *($p<0.001$, one-way ANOVA followed by post hoc Dunnett's test)* in the cortex.
Conclusion: Oral phenytoin and oxybutynin treatment rescued hypoxia-induced hypomyelination in neonatal mice. Due to their established safety profiles in neonates and infants, these medications are promising candidates for treatment of WMI in preterm babies.

Disclosures: L. Odell: None. **S. Panigrahi:** None. **J.R. Chan:** None. **B.E. Ostrem:** None.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.09/R3

Topic: B.09. Glial Mechanisms

Support: Collaborative Center for X-linked Dystonia Parkinsonism (SAL, JDB)
MD Anderson Neurodegeneration Consortium (SAL)
The National Human Genome Research Institute Centers of Excellence in Genomic Science Program (SAL, JDB)
Carol and Gene Ludwig Family Foundation (SAL)
Alzheimer's Association (PP)

Title: Myelin pathology is a key feature of X-linked Dystonia Parkinsonism

Authors: *P. PRAKASH[1], K. LIMBERG[2], W. ZHANG[2], Y. ZHAO[2], A. C. MAR[1], R. BROSH[2], J. D. BOEKE[2], S. A. LIDDELOW[2];
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Abstract: X-linked Dystonia Parkinsonism (XDP) is a severe neurodegenerative movement disorder characterized by progressive motor impairment and selective degeneration of striatal medium spiny neurons (MSNs). XDP is caused by a disease-specific SINE-VNTR-Alu (SVA) retrotransposon insertion in TAF1, a ubiquitously expressed transcription factor. Progress in understanding disease mechanisms has been hindered by the lack of an *in vivo* model and the primate-specific nature of the causative SVA mutation. To overcome these challenges, we generated the first mouse model of XDP by engineering a conditional humanized TAF1 allele containing the disease-causing SVA insertion. Induction of this hybrid gene in $Nestin^+$ neural progenitor cells recapitulated key features of the human disease, including striatal atrophy, progressive motor dysfunction, and reduced survival. Unexpectedly, transcriptomic analysis revealed marked downregulation of genes associated with oligodendrocyte maturation and myelination, implicating glial dysfunction as a previously unrecognized contributor to XDP pathogenesis. Consistent with this findings, XDP mice exhibited increased numbers of $PDGFRA^+$ oligodendrocyte precursor cells and $SOX10^+$ oligodendrocyte-lineage cells within the striatum, suggesting impaired oligodendrocyte differentiation and maturation. Transmission electron microscopy further demonstrated a reduction in myelinated axons and prominent myelin abnormalities, including uncompacted myelin, outfoldings, and ultrastructural disorganization. Importantly, postmortem XDP patient tissue revealed similar pathology, including near-complete loss of myelin in the medial prefrontal cortex adjacent to the corpus callosum. Together, these findings establish the first *in vivo* model of XDP and identify oligodendrocyte dysfunction and myelin pathology as previously unrecognized features of the disease, providing new insight into the cellular mechanisms underlying neurodegeneration in XDP.

Disclosures: P. Prakash: None. **K. Limberg:** None. **W. Zhang:** None. **Y. Zhao:** None. **A.C. Mar:** None. **R. Brosh:** None. **J.D. Boeke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neochromosome, Inc.. F. Consulting Fees (e.g., advisory boards); ReOpen Diagnostics, LLC, Sangamo, Inc., Modern Meadow, Inc., Rome Therapeutics, Inc., Sample6, Inc., Teressa Therapeutics, Inc., Wyss Institute. **S.A. Liddelow:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstronauTx Ltd, SynaptiCure Inc. F. Consulting Fees (e.g., advisory boards); AstronauTx Ltd, BioAccess Fund.

Poster

PSTR046: Oligodendrocytes: Disease Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR046.10/R4

Topic: B.09. Glial Mechanisms

Support: 5R01MH110487-09

Title: Generation and validation of a conditional Arid1b reinstatement mouse model of Coffin-Siris Syndrome

Authors: *S. SHANKARAN[1], J. BOHLEN[2], S. M. STUMP[3], B. J. MAHER[4];
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Abstract: Haploinsufficiency of the ARID1B gene is associated with autism spectrum disorder (ASD), intellectual disability (ID) and Coffin-Siris Syndrome (CSS). CSS is a genetic disorder classified by symptoms of developmental delay, impaired motor skills, low birth weight, ID, and delayed or absent speech and language. Mouse models of CSS harboring germline mutations in Arid1b (Arid1b+/-) are reported to show abnormalities in neuroprogenitor proliferation, deficits in the density of PV+ inhibitory neurons, and behavioral abnormalities related to impaired cognition, abnormal social interaction, and repetitive behaviors. Our lab recently observed that Arid1b mutation also affects the oligodendrocyte (OL) lineage by altering the proportions of oligodendrocyte precursor cells (OPCs), OLs, and the proportion of myelinated axons in the mouse cortex and corpus callosum. Here, we generated a conditional Arid1b reinstatement mouse model of CSS (Arid1bLSL/+), in which a transcriptional STOP cassette and GFP reporter, flanked by loxP sites, was inserted into the first intron of Arid1b. This mouse model allows for visualization of ARID1B-expressing cells throughout the brain and body, and for genetic reinstatement of Arid1b when crossed with promoter-specific Cre recombinase mouse lines. Using qPCR and Western blot, we observed reduced expression of ARID1B in Arid1bLSL/+ mice compared to Arid1b+/+ littermates. Similar to Arid1b+/- mice, in vivo analysis of p24 Arid1BLSL/+ mice confirmed that there was a significant increase in OPCs

(PDGFRα;+) and a significant decrease in mature OLs (CC1+), as well as a significant reduction in the PV+ inhibitory neuron population compared to Arid1b+/+ littermates. We also observed a low percentage of Arid1BLSL/+ mice showing hydrocephalus at similar rates to Arid1B+/- mice, which is a clinical condition found in some human CCS patients. In summary, we have developed and validated a novel mouse model to study cell-type specific reinstatement of Arid1b which will be instrumental in developing therapeutic strategies for CSS and other related ASDs.

Disclosures: S. Shankaran: None. **J. Bohlen:** None. **S.M. Stump:** None. **B.J. Maher:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.01/R5

Topic: C.01. Brain Wellness and Aging

Title: PROLONGED SOCIAL ISOLATION INDUCES AGE-DEPENDENT COGNITIVE IMPAIRMENTS IN MICE

Authors: *C. FRAHM, R. SIMON, M. HAASE;
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Abstract: Social isolation (SI) is increasingly recognized as an environmental stressor associated with adverse cognitive outcomes, with evidence suggesting that susceptibility is particularly heightened during aging. We investigated the effects of 8 weeks of SI on cognitive performance in young (5 months) and aged (22 months) male C57BL/6J/Ukj mice. Cognitive function was assessed during the final two weeksof SI using the Barnes maze. Following SI, both young and aged mice exhibited impaired learning during the 6-day acquisition, reflected by increased latency to reach the escape box. Short-term memory was assessed with the escape box removed and was impaired in SI mice of both ages, as indicated by reduced time at the former target location, with increased latency observed only in aged SI mice. Long-term memory was assessed by retention of the escape box at its original position, and cognitive flexibility by relocation of the target to the opposite position. Both long-term memory and cognitive flexibility were selectively impaired in aged SI mice, reflected by prolonged latencies, with impaired search strategy observed specifically in the long-term memory task.Together, these findings demonstrate that prolonged SI induces age-dependent cognitive impairments. While both young and aged mice exhibited increased latency during learning and the short-term memory task, aging markedly exacerbated deficits in long-term memory and cognitive flexibility. Our results highlight that SI impairs cognition across ages while age remains a critical modifier of susceptibility, indicating that older individuals are particularly vulnerable to its detrimental effects.

Disclosures: C. Frahm: None. **R. Simon:** None. **M. Haase:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.02/R6

Topic: C.01. Brain Wellness and Aging

Support: NSF CAREER Award 2042251

Title: A human-specific brain landmark in aging and cognition

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Abstract: Recent research has uncovered a human-specific brain landmark in a region of the brain responsible for multimodal integration--namely memory, language, communication, and social cognition. Specifically, recent studies identified a distinct, species-specific feature of the human brain located in a portion of the lateral temporal cortex. This human-specific brain landmark is referred to as the superior temporal asymmetrical pit (STAP) given that this structure is consistently deeper in the right compared to the left hemisphere. While the STAP has been shown to relate to functional organization, it has previously only been theorized to relate to individual differences in cognition with no prior evidence to support this theory. Here, we tested if the morphology of this human-specific landmark is related to executive function (UDS3-EF) and language (CDRLANG) in individuals with behavioral variant frontotemporal dementia (bvFTD), primary progressive aphasia (PPA), or healthy (HE) controls (N>100 individuals in each group). After successfully replicating previous results showing that the depth of the STAP is deeper in the right compared to the left hemisphere across each group, we show that the depth of the STAP in the right hemisphere uniquely predicted UDS3-EF beyond other deep sulcal pits-intraparietal sulcus (IPS), inferior frontal sulcus (IFS), and collateral sulcus (COS)-in cognitively normal controls ($F(1,449)=8.36$, $q=0.024$, $\Delta R^2=1.5\%$). In our language analysis, deeper left-hemisphere STAP predicted better language function (lower CDRLANG score) in bvFTD individuals ($\beta=-0.151$, $F(1,253)=10.68$, $q=0.005$, $\Delta R^2=1.6\%$). Exploratory analyses showed that IFS depth in the left hemisphere uniquely predicted UDS3-EF beyond STAP in bvFTD individuals ($F(1,253)=9.49$, $q=0.014$, $\Delta R^2=2.1\%$). No sulcal pit depth tested predicted CDRLANG scores in PPA after correction for multiple comparisons. These findings were independent of age, sex, education, whole-brain volume, and FTLD-CDR sum-of-boxes (FTLD-CDR) severity. To our knowledge, these findings are the first to link this human-specific brain landmark to cognition with insights into aging, as well as theories relating brain structure and function to cognition.

Disclosures: M. Torres: None. **A. Lebron:** None. **A. Hoang:** None. **K.S. Weiner:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.03/S1

Topic: C.01. Brain Wellness and Aging

Support: NIH grant K99AG088064
NIH grant R01AG072893

Title: Lifespan changes in negative affect and functional network correlates in late life

Authors: *S. CHAUDHARY[1], C.-S. R. LI[2];
[1]Psychiatry, Yale Univ. Sch. of Med., New Haven, CT; [2]Psychiatry, Yale Univ., New Haven, CT

Abstract: The "positivity effect" in aging suggests that, compared with younger adults, older adults may experience negative emotions to a lesser extent and may attend to emotional information in a more positive way. Although prior studies support this effect in attention and memory, its relevance to lifespan trajectories of negative affect (NA) remain unclear. Further, given the role of cognition in emotion regulation and its age-related changes, we examined whether cognition moderates lifespan NA changes. We also assessed resting-state functional connectivity (FC) correlates of NA in late life. We used the Aging Adult Brain Connectome (AABC) Release 2 dataset, including 1,155 participants (513 males (M), 642 females (F)) with up to four visits over 8 years. Baseline age ranged from 36 to 100 years (mean ± SD = 60.1 ± 15.3). Cognition and emotion were assessed using the NIH Toolbox. Cognitive scores were summarized into fluid cognition (baseline range: -5 - 2), crystallized cognition (-3 - 2), and memory (-4 - 2) factors. NA scores were standardized to T-scores, with higher scores indicating greater NA (24 - 89). Linear mixed-effects models with subject-level random intercepts were used to examine age-related NA changes across visits. The base model included age, age^2, sex, and retest effects. Cognitive moderation was tested by adding cognition × age and cognition × age^2 interactions. Both the linear (β= -2.51, $p< 0.001$) and quadratic (β = 0.37, $p < 0.001$) age terms were significant, indicating a U-shaped trajectory. NA decreased with age until the early 70s, remained relatively stable thereafter, and then slightly increased after age 80 years. Fluid cognition moderated age-related NA change (linear: β= -0.74, p= 0.012; quadratic: β= 0.13, p= 0.158), whereas crystallized cognition (linear: β= -0.49, p= 0.057; quadratic: β= 0.12, p= 0.169) and memory (linear: β= -0.35, p= 0.195; quadratic: β= 0.07, p= 0.381) did not. Thus, higher fluid cognition was associated with a steeper age-related decline in NA, while the overall nonlinear shape remained similar. In adults>60 years of age (n= 336, age= 74.2 ± 8.3, M/F= 160/176), we identified a network including auditory, cingulo-opercular, frontoparietal, default mode, thalamic, and somatomotor regions with FCs in positive association with NA. The findings were replicated in a testing sample (n= 83, age= 74.1 ± 8.7, M/F= 42/41). Overall, NA followed a nonlinear lifespan trajectory, declining until the early 80s and slightly increasing thereafter. Fluid cognition may support lower NA with age, possibly through more effective emotion regulation. Stronger rsFC within specific networks was associated with greater NA in late life.

Disclosures: S. Chaudhary: None. **C.R. Li:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.04/S2

Topic: C.01. Brain Wellness and Aging

Support: Intramural Research Program of the NIH, National Institute on Aging

Title: Mosaic neuronal architecture of multidimensional cognitive aging in Long-Evans rats

Authors: *S. DUTTA GUPTA[1], K. HUILLCA-JARA[1], T. SWIATKOWSKI[2], E. PEREZ[3], J. M. LONG[4], P. R. RAPP[5];
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Abstract: Aging is marked by heterogeneity in cognitive and socioemotional outcomes, yet cellular features distinguishing resilient from vulnerable late-life phenotypes remain poorly defined. Social cognition is a key determinant of healthspan and neuropsychiatric risk, but its biological substrates in aging remain poorly understood. We previously found that aged rats show variability in social novelty preference that is dissociable from hippocampal-dependent spatial memory. Here, we asked whether social and spatial outcomes in aging map onto cellular signatures across oxytocin signaling, inhibitory interneurons, and perineuronal net (PNN)-associated extracellular matrix remodeling. Young (6-month) and aged (24-month) male Long-Evans rats were behaviorally characterized for spatial memory in the Morris water maze and social novelty preference in the three-chamber task. We examined cellular systems positioned to regulate social and mnemonic circuitry, including oxytocin signaling, parvalbumin (PV) and somatostatin (SOM) interneurons across prefrontal and dorsal hippocampal subregions, and PNNs in hippocampal CA2. Aging produced a mosaic pattern of cellular vulnerability and resilience. PVN oxytocin cell counts and plasma oxytocin levels were preserved, whereas prefrontal oxytocin receptor (OXTR) expression was reduced and its association with novel social investigation was affected in aged rats. Hippocampal OXTR was preserved, indicating circuit-specific oxytocin-system remodeling. SOM interneuron counts were preserved across prefrontal and hippocampal regions, yet dentate gyrus SOM counts tracked spatial memory among aged rats, implicating this population in cognitive resilience. In contrast, PV interneurons showed selective hippocampal vulnerability, with reductions across the pyramidal cell fields but sparing in the dentate gyrus and prefrontal cortex. PV loss marked hippocampal aging, while PV-associated PNN immunoreactivity intensity in CA2 revealed extracellular matrix remodeling. Notably, PV-associated PNN intensity was associated with social novelty, but not spatial memory. This domain-specific relationship mirrors the phenotypic dissociation between social novelty and spatial memory, suggesting that PV-PNN remodeling may contribute selectively to social vulnerability in aged rats, Together, these findings support a model in which late-life vulnerability is shaped by region- and circuit-specific cellular remodeling rather than uniform decline, with CA2 PV-PNN integrity emerging as a novel substrate of social aging.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.05/Web Only

Topic: C.01. Brain Wellness and Aging

Title: The Role of Obesity and Physical Activity in the Relationship Between Depression and Cortical Thickness in Cognitively Unimpaired Older Adults

Authors: *P. WALSH[1], D. LUU[1], M. DAVISON[1], A. W. TOGA[1], S. O'BRYANT[2], K. YAFFE[3], M. N. BRASKIE[1];
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Abstract: Depression has been associated with an increased risk of dementia, including AD, which is possibly driven by cortical thinning. It is also linked to higher obesity levels and lower physical activity, both of which contribute to cortical thinning. However, it is unclear if both mediate the relationship between depression and cortical thickness, particularly in brain regions vulnerable to AD-related neurodegeneration. We analyzed T1-weighted MRI data collected by Siemens 3T MRI scanners from 2631 cognitively unimpaired participants in the Health and Aging Brain Study - Health Disparities (mean age: 64.90 ± 8.36). FreeSurfer was used to calculate cortical thickness in the inferior temporal (IT), middle temporal (MT), superior temporal (ST), entorhinal (EC), and parahippocampal (PC) cortices. Depression severity was assessed using the Geriatric Depression Scale (GDS). Obesity and physical activity were measured using Body Mass Index (BMI) and the Rapid Assessment of Physical Activity (RAPA) questionnaire, respectively. We used linear regression to assess whether GDS scores predicted cortical thickness, with and without adjustment for BMI and RAPA. Mediation analyses and structural equation models (SEM) were used to evaluate the indirect effects of BMI and RAPA on the relationship between depression and cortical thickness. Covariates included age, sex, APOE4 positivity, ethnoracial group, education, income, and MRI scanner. P-values were FDR-corrected across regions. Higher GDS scores were associated with a thinner IT cortex ($p = 0.015$; $\beta = -0.058$). After adjusting for BMI and RAPA, the relationship was attenuated to trend-level significance ($p = 0.057$; $\beta = -0.050$). While mediation analyses suggested an indirect effect of BMI on the relationship between depressive symptoms and IT cortical thickness ($p = 0.017$; $\beta = -0.003$), SEM demonstrated trend-level significance when both BMI and RAPA were included as mediators ($p = 0.092$; $\beta = -0.003$). No significant mediation effect was observed for RAPA ($p = 0.070$; $\beta = -0.005$). Depressive symptoms are associated with reduced thickness in the IT cortex, an area in the brain vulnerable to AD-related neurodegeneration, with obesity serving as a

potential mediator in this specific relationship. These findings support a possible link between depression, metabolic health, and neurodegeneration in dementia-related disorders.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.06/S3

Topic: C.01. Brain Wellness and Aging

Title: Cognitive performance and its relationship with education, depression, life satisfaction and daytime sleepiness. A communitary study.

Authors: *L. ENRICH PIZA;
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Abstract: Authors: Enrich Piza, L1 , Ramos Languren LE2, Lomelí González, J1, González Piña, R 3 1Instituto Politécnico Nacional, 2 Facultad de Psicología UNAM and CLIREDACE HIGG, 3 Instituto Politécnico Nacional and CLIREDACE HIGG. **Background:** Cognitive performance in aging could be affected by psychosocial factors like gender, age, level of education, life satisfaction, daytime sleepiness and depression. This exploratory study had the aim to describe the cognitive performance in Mexican older adults, and analyze the cognitive performance according to variables like gender, age, educational level, life satisfaction, daytime sleepiness and depression. **Methods:** The study recruited 71 participants from nursing homes with an age range of 60 to 92 years old (43 female, 28 male). Participants had to complete the Montreal Cognitive Assessment (MoCA), version 8.1 Spanish, the Beck Depression Inventory, the Epworth Sleepiness Scale and the Index for Life Satisfaction. Descriptive analysis, independent t-tests samples and Pearson correlations were conducted. **Results:** The Montreal Cognitive Assessment MoCA scores showed that 2.8% of the participants scored within severe cognitive impairment, 7% with moderate cognitive impairment, 60.6% with mild cognitive impairment and 29.6% with normal cognitive performance. There were no significant differences for sex and age, MoCA, depression or life satisfaction scores. In women results show a negative correlation for MoCA Scores and age ($r = -.430$, $p = 0.004$) and a positive correlation for MoCA Scores and years of study ($r = .460$, $p = 0.002$). In men, results showed a positive correlation for MoCA scores and years of study ($r = .390$, $p = 0.04$) and a negative correlation for MoCA scores and Epworth Sleepiness Scale ($r = -.393$, $p = 0.038$). **Conclusion:** Cognitive performance was associated with a higher level of education, supporting the role of the cognitive reserve during aging. Older women showed lower cognitive performance as well as men that present greater daytime sleepiness. The findings suggest that the amount of years and daytime sleepiness influence cognitive performance in Mexican older adults.

Disclosures: L. Enrich Piza: None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.07/S4

Topic: C.01. Brain Wellness and Aging

Support: NINDS IRP

Title: Aging related changes in cholinergic inputs to the hippocampus and social learning

Authors: *G. WATKINS[1], S. DIMOVA[2], D. A. TALMAGE[3], L. W. ROLE[4];
[1]LCSMS, NIH/NINDS, Bethesda, MD; [2]Intl. Max Planck Res. Sch. for Synapses and Circuits, Jupiter, FL; [4]NINDS, [3]NINDS, Bethesda, MD

Abstract: The CA2 subregion of the hippocampus is necessary for the proper acquisition and expression of many fundamental social behaviors including familiarization and recognition, threat detection, and the establishment of hierarchies; however, the way these behaviors are established and modulated remains less well understood. Acetylcholine release from basal forebrain cholinergic neurons (BFCNs) to different regions of the hippocampal formation has been shown to contribute to diverse forms of learning including spatial navigation and threat memory encoding, and aging-related changes in cholinergic innervation are associated with declining cognition and memory. In this study we address the contributions of cholinergic inputs from the medial septum and the vertical limb of the diagonal band of Broca (MS/DB) to the CA2 subfield in social behavior. Additionally, we ask whether the MS/DB inputs to CA2 change across the lifespan and how, if at all, alterations in the integrity of this innervation pathway affect social memory.
We used a classic three-chamber test to assay social preference in both mature adult (12-16 weeks) and old (82-86 weeks) mice. Subsequently, we performed immunohistochemistry experiments on these mice to compare cFos activity in both the MS/DB and CA2 regions and looked for potential degradation of either the cholinergic cell bodies or axonal fields in old animals. Young animals displayed a strong preference for the novel subject; this preference was eliminated when cholinergic signaling from MS/DB was blocked during the initial interaction phase of the three-chamber test. Old animals showed a reduced preference for the novel subject despite similar overall sociability, suggesting a potential deficit in recognition of familiar subjects. Old animals also had decreased numbers of BFCNs, and decreased activity in CA2, suggesting that changes in cholinergic signaling during aging might contribute to alterations in social behavior.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.08/S5

Topic: C.01. Brain Wellness and Aging

Title: Fixel-Based White Matter Differences Across the Lifespan and their relationship to trust.

Authors: *J. F. FOLEY[1], S. J. LYONS[2], B. E. DEPUE[2];
[1]Psychological & Brain Sci., Univ. of Lousiville, Louisville, KY; [2]Psychological & Brain Sci., Univ. of Louisville, Louisville, KY

Abstract: Older adults are frequently targeted by scamming operations which cause significant harm to quality of life to a vulnerable population. Changes to white matter integrity among older adults are well established, alongside changes to executive functioning and sensory integration. However, the relationship between white-matter integrity and interpersonal dynamics among older adults remains poorly understood. Furthermore, studies on white matter structure have traditionally used metrics like functional anisotropy (FA) to measure WM structure. To address this, we used open-source data (Smith et al., 2024; OpenNeuro/ds005123) of 101 participants aged 21 to 80 (M = 43.3, SD = 17.5) that received both a T1w structural scan, a high angular resonance diffusion image (HARDI) scan, and completed the trust task. The structural scans were processed, segmented, and intercranial volume (ICV) was estimated using FreeSurfer. MRTrix3 was used to preprocess the HARDI scans and estimate fiber orientation distributions. We then used the fixel-based analytical (FBA) method to analyze 3 metrics of white matter microstructure: fiber density (FD) and fiber cross-section (FC). The sample was broken down into 3 age groups and t-tests between age groups were conducted using GLMs for each metric using the connectivity-based fixel enhancement (CFE) method, with each accounting for the covariates of sex and ICV; however, as FC is on a log scale, ICV was log transformed. All significant fixels were corrected for multiple comparisons at $p < 0.05$. For the FD metric, significant differences were seen in the left superior longitudinal fasciculus (SLF) for old adults compared to middle-aged adults as well as in the brainstem and corpus callosum (CC) compared to young adults. Interestingly, older adults showed significant FC differences in the cerebrospinal tract (CST) compared to both middle-age and young adults. In addition, significant differences in FC were seen in the right parietal WM in young compared to middle-aged adults. To investigate at the association between trust and WM, we regressed significant fixels from the old versus middle contrast with trust ratings from the trust game. CFE based regression showed no significant association between trust and significant FD in older compared to middle-aged adults. Together our results show that there are unique micro and macrostructural differences in WM across the lifespan. While trust ratings did not significantly relate to the underlying FD of the WM, more advanced modelling techniques like general additive models may better capture the relationship between trust, covariates, WM structural measures.

Disclosures: J.F. Foley: None. **S.J. Lyons:** None. **B.E. Depue:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

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Program #/Poster #: PSTR047.09/S6

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant U01MH110274

Title: The Normative Aging Process of Brain Functional Synergy and Redundancy

Authors: *W. YIN[1], W. LIN[2];
[1]Univ. of North Carolina, Chapel Hill, NC; [2]Univ. North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Background: Traditional FC analyses quantify statistical dependencies between brain regions but provide limited insight into the informational structure of BOLD signals. Information-theoretic decomposition separates neural interactions into synergistic components linked to higher-order cognition and redundant components associated with sensorimotor processing. However, normative aging trajectories of synergy and redundancy remain undiscovered. Here, we constructed normative charts of synergy and redundancy across aging and examined their associations with cognitive performance. **Methods:** We analyzed data from the HCP-Aging and AABC cohorts (1339 subjects, 2633 visits; 35-90 years). BOLD signals were extracted from Schaefer200 atlas following conventional fMRI preprocessing. Using integrated information decomposition, pairwise interactions were separated into synergistic and redundant components. Whole-brain and network-level metrics were calculated as mean value across whole-brain and functional networks. GAMLSS was used to model age-related trajectories. Individual deviations from normative trajectories were further used to predict NIH Toolbox cognitive performance. **Results**: Whole-brain and network-level synergy remained relatively stable from 35 to 60 years of age, except in sensorimotor, and then declined in later life. In contrast, redundancy exhibited relatively modest age-related changes, except in the visual, sensorimotor, and ventral attention networks (Fig. 1a). Cognitive performance demonstrated widespread positive associations with synergistic interactions, while redundant interactions showed weaker and more heterogeneous relationships (Fig. 1b). Repeated nested 10-fold cross-validation (100 times) further demonstrated that synergy and redundancy metrics could reliably predict cognitive performance (Fig. 1c). **Conclusion:** Our study characterized normative aging trajectories of brain synergy and redundancy and demonstrated their potential utility as biomarkers for monitoring cognitive function during aging.

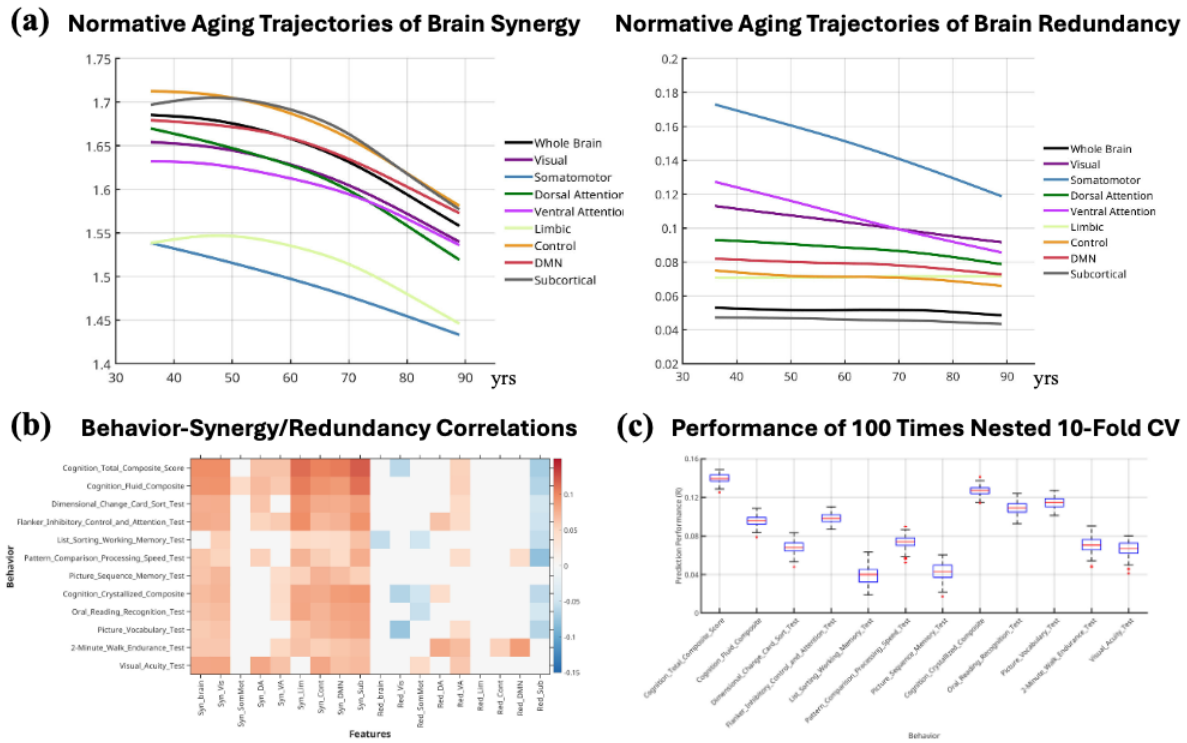


Figure 1. (a) Normative aging trajectories of whole-brain and canonical network-level functional synergy and redundancy (GAMLSS model). (b) Associations between whole-brain and network-level synergy/redundancy and cognitive performance measured by the NIH Toolbox ($p<0.05$, FDR corrected). (c) Prediction performance of cognitive function based on brain synergy and redundancy metrics, evaluated using elastic-net regression with 100 iterations of nested 10-fold cross-validation.

Disclosures: W. Yin: None. **W. Lin:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.10/S7

Topic: C.01. Brain Wellness and Aging

Title: Successful Encoding-Related fMRI Activity at Baseline Predicts Future Memory Aging

Authors: *B. P. PATWARDHAN[1], F. DIARRA[2], X. CHEN[3];
[2]Psychology, [1]Stony Brook Univ., Stony Brook, NY; [3]Psychology, Stony Brook Univ., Centerport, NY

Abstract: Memory decline is common in aging, but underlying neural mechanisms are still unclear. To examine the neural activity pattern driving different memory trajectories, we assessed baseline brain activation during memory, using subsequent memory task fMRI data from 421 individuals across the adult lifespan, and longitudinal prospective memory change,

using three waves of episodic memory data, in the Dallas Lifespan Brain Study. For fMRI, we focused on the subsequent memory effect (SME) contrasting trials subsequently remembered with high confidence against those later forgotten. We found positive SME activation in bilateral occipital, temporal, fusiform, and inferior frontal regions, and negative SME (i.e., suppression) in regions largely comprising the default mode network (Fig1a). Increasing age was related to lower positive SME and less negative SME (Fig1b). Participants were divided into young (21-40 yrs; n=84), middle-aged (40-65 yrs; n=152), and old (65-89 yrs; n=185) groups. Whole-brain analysis examined voxel-wise associations with baseline memory performance or prospective memory slope (Fig1f) in each group while controlling for age. Baseline memory composite was positively related to SME in young adults in left hippocampus (Fig1c). Prospective memory slope was positively related to SME in left mid/superior temporal gyrus in the middle-aged group (Fig1d) where higher SME predicted better longitudinal memory maintenance. Interestingly, prospective memory slope was negatively related to SME in inferior and middle frontal gyri in young adults (Fig1e): higher SME at baseline was associated with faster memory decline. All results were significant after cluster-wise FWE correction with initial voxel threshold at $p < .001$. In conclusion, we found that activation and suppression are essential for successful encoding, and both of these decrease with age, supporting neural de-differentiation in aging. Higher activation in middle-aged adults is predictive of future memory maintenance and may suggest midlife as a critical period as cognitive aging begins to diverge.

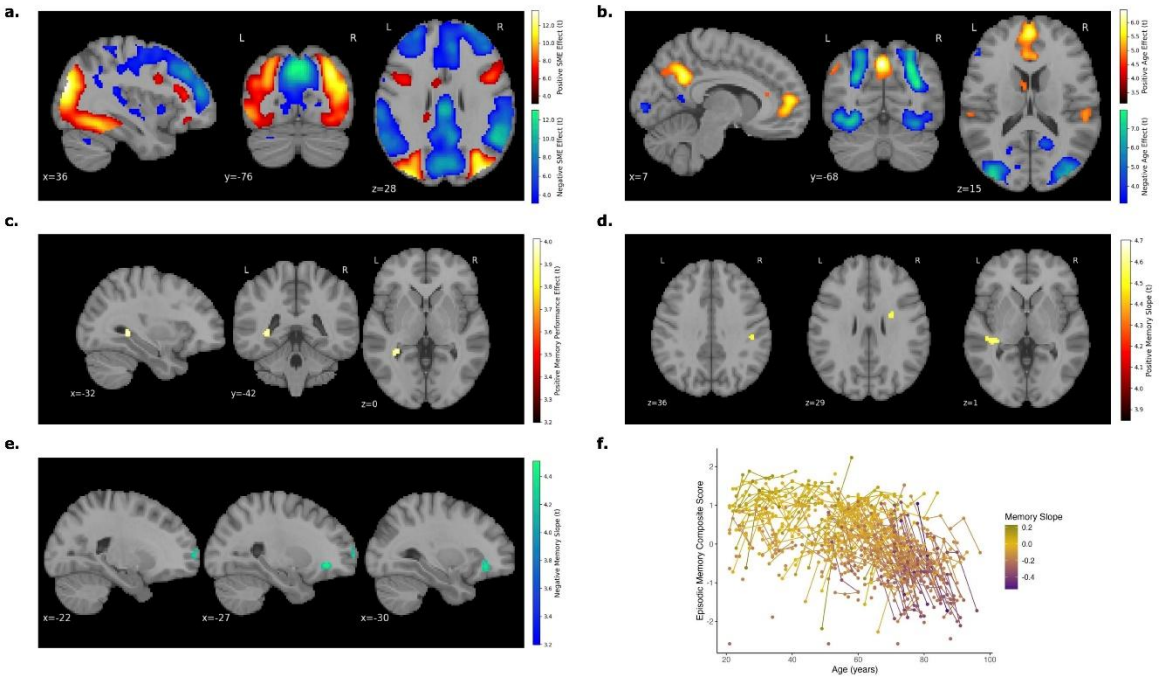


Figure 1. **a**. Subsequent memory effect (SME), defined as high-confidence hit > miss, observed positively in lateral temporal, mid/lateral occipital, and prefrontal regions and negatively in default mode regions, after FWE correction. **b**. SME in task-positive regions decreases in aging, whereas negative SME becomes less negative with age, after FWE correction. **c**. In the Young group (21-40 yrs), SME was positively related to baseline memory performance in the left hippocampus. **d**. In the Middle-aged group (40-65 yrs), individuals with higher baseline fMRI activity in temporal clusters had better longitudinal memory maintenance, after FWE cluster correction. **e**. In Young group (21-40 yrs), higher baseline SME in prefrontal clusters was related to prospective memory decline. **f**. Memory changed significantly in three visits over 12 years, showing large inter-individual variability. For visualization purposes, all brain maps are thresholded at k>15.

Disclosures: B.P. Patwardhan: None. **F. Diarra:** None. **X. Chen:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.11/S8

Topic: C.01. Brain Wellness and Aging

Support: University of Oklahoma Dodge Family College of Arts and Sciences

Title: Choline and Iron in Cognitive Function: Associations With Cognitive Impairment in Older Adults, From NHANES 2011-2014

Authors: *I. RAY[1], M. J. WENGER[2];
[1]Neurolog. Surgery, Weill Cornell Med., New York, NY; [2]Ctr. for Applied Social Res., Univ. of Oklahoma, Norman, OK

Abstract: Cognitive reserve is hypothesized to reflect the brain's ability to maintain function despite neuropathological changes. Choline supports acetylcholine synthesis, membrane integrity, and methylation, all of which have been suggested to contribute to cognitive reserve. In contrast, iron accumulation in aging contributes to oxidative stress, neuroinflammation, and neuronal injury. Our study examined the combined roles of dietary choline intake and iron status in cognitive impairment and tested whether choline moderates iron-related cognitive effects. We conducted a cross-sectional analysis of NHANES 2011-2014 data from adults aged ≥60 years (n = 2,502; 54% male; mean age 69.3 ± 6.8 years). Cognitive outcomes included mild and moderate cognitive and memory impairment assessed using CERAD word learning, animal fluency, and digit symbol substitution tests. Iron exposure was assessed by serum biomarkers and dietary intake and choline intake were assessed using 24-hour dietary recalls. Exposures were categorized into tertiles. Multivariable logistic regression models adjusted for demographic, socioeconomic, health, and lifestyle covariates, and iron×choline interaction terms were tested. Low choline intake was consistently associated with higher odds of cognitive impairment across all outcomes, with the strongest associations observed in the lowest intake group compared with the highest (mild memory impairment OR≈1.6; 95% CI 1.25-2.1; mild cognitive impairment OR≈1.9; 95% CI 1.3-2.6; moderate cognitive impairment OR≈2.5; 95% CI 1.6-4.0). Higher iron intake and biomarker levels showed inverse or weak associations in unadjusted models which were attenuated and nonsignificant after adjustment. Importantly, no significant iron×choline interactions were detected, suggesting that the association between choline intake and cognitive impairment is independent of iron status. Overall, the findings indicate that iron-related physiology and choline availability are relevant to cognitive aging with low dietary choline intake showing strong independent association with increased odds of cognitive impairment in this nationally representative sample of older adults. This supports the importance of adequate choline intake in maintaining cognitive health, with limited evidence for interaction with iron status in this cohort.

Disclosures: I. Ray: None. **M.J. Wenger:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.12/T1

Topic: C.01. Brain Wellness and Aging

Title: Vascular White Matter Injury Selectively Weakens Default Mode-Dorsal Attention Network Segregation Independent of Aging

Authors: *N. K. GUPTA, V. TIWARI;
Indian Inst. of Sci. Educ. and Res. (IISER) Berhampur, Berhampur, India

Abstract: White matter hyperintensities (WMHs), periventricular (PVWMH) and deep WMH (DWMH), represent one of the most prevalent forms of vascular brain insult in aging and mark fiber loss and neuroanatomic injury. We examined whether progressive WMH burden alters Default Mode, Dorsal Attention and Salience network organization, neural dynamics, and cognition beyond chronological aging. Because PVWMH and DWMH differ in anatomy and vascular supply, we further tested whether they exert distinct effects on network architecture and executive function, given prior evidence that PVWMH burden predicts attentional decline, executive dysfunction, and higher brain age.
Longitudinal resting-state fMRI from 212 cognitively normal (CN) adults in ADNI3 (563 visits; age 55-95 years; 97 men, 115 women) was complemented by an independent cross-sectional lifespan cohort of 320 CN (age 20-65 years), with an auditory oddball task-fMRI subset (n=30) and a mild cognitive impairment subgroup. WMH burden increased exponentially, with PVWMH rising from 5.01±6.4 to 6.72±7.8 mL and DWMH from 2.23±3.7 to 2.80±4.5 mL. Across mixed-effects and generalized additive models controlling for age and repeated measurements, PVWMH, but not DWMH, was the dominant predictor of reduced DMN-DAN segregation, especially increased lateral parietal-intraparietal sulcus connectivity (β=0.009, p=0.002), an effect reproduced in the independent cohort, preserved in MCI, and robust to sleep-duration adjustment. Greater LP-IPS coupling was associated with slower Trail Making Test-B performance (β=17.74, p=0.007), linking network dedifferentiation to executive dysfunction. PVWMH also increased BOLD entropy in DAN regions, whereas DWMH preferentially reduced entropy in salience nodes (anterior insula) and produced broader, more distributed cortico-subcortical reorganization. These findings indicate that lesion topography matters: PVWMHs appear to drive an IPS-centered breakdown of DMN-DAN antagonism and attentional dynamics that tracks with poorer executive control, whereas DWMHs exert more modest and anatomically diffuse effects. Scientific rigor was strengthened by longitudinal replication, an independent cohort, cross-modal task validation, lesion-compartment stratification, and model adjustment for age, sleep duration and within-subject dependence.

Disclosures: N.K. Gupta: None. **V. Tiwari:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.13/T2

Topic: C.01. Brain Wellness and Aging

Support: Alzheimer's Association 25AARG-1413315
NIH Grant R00MD0169640

Title: Ancestry-associated regulatory aging of the Black American brain converges on immune RNA programs

Authors: O. PERLOFF[1], A. BENNETT[2], ***K. J. BENJAMIN**[2];
[1]Northwestern Univ., Evanston, IL; [2]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Black Americans experience disproportionate risk of Alzheimer's disease and related dementias (ADRD), yet individuals of African ancestry remain underrepresented in functional genomic studies of the human brain. This gap limits our understanding of how aging modifies ancestry-associated regulatory programs that may contribute to brain vulnerability. We profiled postmortem RNA-sequencing from Black/African American neurotypical donors across the hippocampus (N = 123), caudate nucleus (N = 120), and dorsolateral prefrontal cortex (DLPFC; N = 121) to define how genetic ancestry and age jointly shape gene regulation across expression, isoform, splicing, and usage phenotypes. Age-dependent ancestry-associated regulation was widespread, most pronounced at the gene-expression level in the caudate, and extended broadly across RNA-processing layers. Splicing, isoform abundance, and transcript-usage effects implicated many genes not detected by gene-level expression alone, indicating that ancestry-associated regulatory aging is organized through coordinated changes in RNA processing as well as total abundance. These effects were most strongly shared between DLPFC and hippocampus, with lower sharing between caudate and either cortical region, yet all regions converged on immune and inflammatory programs enriched for glial and immune cell-type markers. Estimated cell-type composition showed no significant ancestry-by-age interaction, and sensitivity analyses indicated that the observed regulatory patterns were not explained by detectable bulk compositional shifts. Allele-specific expression supported a contribution of cis-regulatory mechanisms, while gene-set and stratified heritability analyses connected interaction-associated regulatory features to neurological and neuropsychiatry genetic risk. Together, these findings identify glial and immune RNA regulation as a major axis through which aging modifies ancestry-associated regulatory architecture in the human brain, providing a framework for ancestry-informed studies of ADRD vulnerability.

Disclosures: O. Perloff: None. **A. Bennett:** None. **K.J. Benjamin:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.14/T3

Topic: C.01. Brain Wellness and Aging

Title: Divergent compensatory mechanisms underlie sex differences in vascular brain aging

Authors: *S. YAGHOOBI[1], Y. ZARRABI[3], C. PLOESSL[2], A. ROMANOWSKI[2], C. KAUR[4], F. SOROND[5];
[1]Neurol., [2]Northwestern Univ., Chicago, IL; [3]Loyola Univ., Chicago, IL; [4]Loyola Univ. Chicago, Chicago, IL; [5]Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: White matter hyperintensities (WMH) predict cognitive decline, but the drivers of sex-dependentdifference are unknown. We used data from 750 cognitively healthy older adults (65.8±7.7y; 62%female) with multimodal imaging data including cortical, hippocampal and WMH volumes,hippocampal Amplitude of Low-Frequency Fluctuations (mALFF), and functional connectivity(FC of 11 resting-state networks) and cognitive measure across 4 domains, to close this knowledgegap. Our results show similar WMH burden (mean 0.77±0.66% ICV, p=0.855) and WMH-drivenhippocampal atrophy across sexes (females: β=−0.177; males: β=−0.290, both p<0.001, sex differences p=0.1), but only males had significant WMH-related cognitive decline (β=−0.317,p<0.001). Using a sex-stratified parallel, serial, and moderated mediation full covariate adjustedanalyses, we observe that in males (n=287), hippocampal atrophy mediated WMH-relatedexecutive function decline (indirect β=−0.057 Bootstrap 95%CI [−0.114,−0.014], p=0.007) andcortical volume mediated processing speed decline (β=−0.046 [−0.101,−0.008], p=0.016). Critically, WMH-driven hippocampal atrophy triggered local amplitude upregulation(mALFF↑) that partially offset cognitive decline via a serial compensatory chain (β=+0.007[0.001,0.021], p=0.020); entirely absent in females. In females (n=463), hippocampal and corticalmediation pathways were fully absorbed by vascular risk covariates (hypertension 60%; CAD16%), becoming non-significant upon their inclusion, revealing FC as the operative mechanism.At preserved FC (+1SD), the WMH→hippocampal atrophy→cognition pathway was completelyattenuated (β=−0.014, p=0.324); at compromised FC (−1SD), structural damage translated directlyinto cognitive decline (β=−0.035, p=0.016). Males showed zero FC moderation; their structuralpathway persisted identically across all FC strata (β≈−0.069, all p<0.014), with FC levels non-significantly different between sexes (p=0.159). Our data suggest sex-dependent divergingintermediate pathways, where males exhibit FC-independent structural vulnerability withhippocampal hyperactivation as compensatory reserve, while females rely on functional networkintegrity as their primary buffer against vascular brain injury.

Disclosures: S. Yaghoobi: None. **Y. Zarrabi:** None. **C. Ploessl:** None. **A. Romanowski:** None. **C. Kaur:** None. **F. Sorond:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.15/T4

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 1R56AG060052-01

Title: Machine Learning Models Collectively Identify Predictive Brain Activation Patterns of Older Adults' Working Memory Performance

Authors: *Y. LIU, C. BASAK;
Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX

Abstract: Previous work has shown that older adults exhibit altered neural recruitment during working memory (WM), including reduced task-positive activation and inefficient overactivation relative to younger adults, especially in the frontal cortex (Qin & Basak, 2020; Skolasinska et al., 2024). However, group-level activations do not reveal how these neural patterns explain individual differences in older adults' cognition. In the current study, we used machine learning (ML) models to move from localization to source-level prediction of older adults' WM performance. We analyzed fMRI-BOLD and behavioral data from 24 younger adults (18-30 years) and 56 older adults (65+ years) who completed a random N-Match WM task crossing WM load (0-, 2-, 3-Match) with stimulus domain (verbal, visual). ROIs were derived from group-level activation sources: Young > Old, Old > Young, young-defined, and combined-age contrasts. Within older adults, block-level ROI features were extracted as mPSC differences for: 1) the overall WM effect relative to perceptual-motor processing (2- & 3-Match > 0-Match), and 2) the incremental WM load effect (3-Match > 2-Match). WM performance included: 1) *d'* for memory sensitivity, and 2) Inverse Efficiency Score (IES) for accuracy-RT efficiency. We tested whether each ROI source predicted 2- and 3-Match WM performance beyond demographic covariates: age, sex, education, and BMI. Three complementary ML models were compared: Ridge regression, partial least squares regression (PLSR), and principal component regression (PCR). Model performance was evaluated using nested repeated cross-validation, with out-of-fold prediction accuracy quantified as the Pearson correlation between predicted and observed behavior. Across models, the strongest and most consistent predictive source was the Young > Old ROIs. It predicted *d'* and IES across 2- and 3-Match conditions, with the best prediction accuracy reaching $r = .470$ for *d'* and $r = .487$ for IES. This was followed by combined-age and young-defined ROIs, with Old > Young ROIs showing the weakest prediction. The most consistent contributors included paracingulate gyrus, insular cortex, and superior frontal gyrus features, implicating frontal cognitive-control regions and the insular cortex. Both the overall WM effect and incremental load effect contributed to prediction, suggesting that performance-relevant activation captured two aspects of task demand: the shift from perceptual-motor processing to cognitive control, and further neural recruitment as WM load increased. Follow-up analyses will test robustness with permutation and profile neural patterns using Young > Old ROI-based clustering.

Disclosures: Y. Liu: None. **C. Basak:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.16/T5

Topic: C.01. Brain Wellness and Aging

Support: Canadian Institutes of Health Research (CIHR) Project Grant operating grant (MOP180400)
CIHR Mid Career Investigator Prize in Research in Aging (MOP179758)
University of Alberta Graduate Recruitment Scholarship

Title: Contributions of hippocampal white matter connections to episodic memory function across the human adult lifespan

Authors: *G. NASR[1], J. SERRANO[2], S. HRYBOUSKI[2], E. HERNANDEZ[1], M. CAHILL[1], P. SERES[3], N. MALYKHIN[2];
[1]Neurosci. and Mental Hlth. Inst., [2]Psychiatry, [3]Radiology & Diagnos. Imaging, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Background: Healthy aging affects hippocampal structure, its connectivity, as well as visuospatial memory performance. The fimbria, fornix, and parahippocampal cingulum (PHC) are the major hippocampal white matter tracts. Past diffusion tensor imaging (DTI) studies analyzed the fornix and fimbria as a single tract, masking the potential contributions of each white matter tract to memory function. In the present study, we applied reliable tractography protocols subdividing the fornix into the body, crus, anterior and posterior columns, and fimbria to investigate the effect of age and their individual contributions to visuospatial memory performance across the adult lifespan. We also determined their associations with hippocampal volumes.
Methods: We recruited 118 healthy volunteers (20-93 years old). T1-weighted and DTI datasets were acquired on a 3T Siemens scanner. Deterministic tractography was done in DSI Studio to estimate fractional anisotropy (FA), radial diffusivity (RD), tract volume, and mean length (ML). The hippocampus and its subregions were segmented via Automated Segmentation of Hippocampal Subfields (ASHS). Immediate and delayed episodic memory were assessed with Designs I and II subtests of the Weschler Memory Scale IV respectively. Regression modeling and partial Pearson correlations adjusted for age were used to examine the links between age, DTI metrics, hippocampal volumetrics, and memory scores.
Results: FA decreased linearly in the body and columns of fornix (ps<0.018), while in the crus, fimbria, and PHC FA reduction was nonlinear (ps<0.001). RD increased nonlinearly in the body and crus of fornix, fimbria, and PHC (ps<0.001), while in the anterior columns RD increased linearly (p=0.044) but it was unchanged in the posterior columns. Volume of all hippocampal connections declined nonlinearly with age (ps<0.001). Age showed negative linear associations with ML in the posterior columns and fimbria (ps<0.001) and nonlinear associations in the body, crus, and PHC (ps<0.013). ML was preserved in the anterior columns. Tract volumes of the body and crus of fornix, fimbria, and PHC correlated with hippocampal volume, its anterior and posterior subregions (ps<0.024). Better performance on immediate memory tests was linked to

crus of fornix volume, FA, RD, and PHC ML (*p*s<0.043). Better performance on delayed memory tests was linked to higher FA in the body and crus of fornix, and lower RD in the posterior columns (*p*s<0.029).
Conclusions: Our results suggest a differential impact of healthy aging on hippocampal white matter tracts, as well as showing their individual contributions to visuospatial memory function independent of age.

Disclosures: G. Nasr: None. **J. Serrano:** None. **S. Hrybouski:** None. **E. Hernandez:** None. **M. Cahill:** None. **P. Seres:** None. **N. Malykhin:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.17/T6

Topic: C.01. Brain Wellness and Aging

Support: Canadian Institutes of Health Research (CIHR) Project Grant (MOP180400) and CIHR Mid-Career Investigator Prize in Research in Aging (MOP179758) PI - Dr. N. Malykhin.

Title: Contributions of prefrontal white matter connections to executive functions, processing speed, and memory performance in healthy cognitive aging

Authors: *N. MALYKHIN[1], E. FUJIWARA[2], W. PIETRASIK[1];
[1]Psychiatry, [2]Psychology, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Background: The prefrontal cortex (PFC) is especially vulnerable to the effects of age. Executive functions (EF) are dependent on the PFC. Age-related decline in EF, working memory, and processing speed could be linked to the preferential deterioration of the PFC and its white matter connections. The main goal of the present study was to determine how white matter microstructure and macrostructure of different PFC subregions support cognitive functions in healthy cognitive aging. **Methods:** A total of 140 healthy adults (aged 18-85) were recruited for this study and completed Magnetic Resonance Imaging (MRI) scan. We used reliable deterministic diffusion tensor imaging (DTI) tractography protocols to segment PFC white matter into medial and lateral orbitofrontal (OFC), medial prefrontal, and dorsolateral prefrontal (DLPFC) subregions. We examined microstructural (fractional anisotropy, axial and radial diffusivities) and macrostructural DTI measures (tract volume, fiber counts, fiber length, number of fibers per voxel) in each PFC subregion. Executive functions were examined using the Delis-Kaplan Executive Functions System. Memory performance was assessed using the Wechsler Memory Scale, the California Verbal Learning Test, and the Paced Auditory Serial Addition Test. Simple and choice reaction time measures were obtained using the Deary-Liewald Reaction Time Task. **Results:** Increased age was associated with decline in processing speed (Pearson r=-0.657, p<0.001), executive functions (r=-0.659, p<0.001), auditory working memory (r=-0.205,

p=.015), visual working memory (r=-0.746, p<0.001), verbal memory (r=-0.533, p<0.001), and visuospatial memory (r=-0.720, p<0.001). White matter microstructural properties of the PFC tracts were not related to cognitive functions after controlling for age. In contrast, macrostructural properties of PFC white matter tracts predicted cognitive functions independently of age. Fiber count, number of fibers per voxel, and tract volume of the DLPFC white matter tracts were linked to better performance on EF tasks, auditory and visuospatial working memory. Fiber length of the DLPFC and medial OFC white matter tracts also predicted performance on EF tasks, processing speed, auditory/visuospatial working memory, and delayed visuospatial memory. **Conclusions:** Our results provide initial evidence for associations between PFC macrostructural integrity and cognitive functions across the adult lifespan. Our findings suggest that DLPFC and medial OFC white matter connections may play a key role in maintaining performance across multiple cognitive domains.

Disclosures: N. Malykhin: None. **E. Fujiwara:** None. **W. Pietrasik:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.18/T7

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant 1R56AG060052-01
Faculty Research Initiative Grant from UTD

Title: Unpredictable Probe-Switching during Working Memory Training Restores Age Deficits in Memory-Sensitive Cortical Activation

Authors: C. BASAK[1], ***J. DODGEN**[2], S. PANDA[2];
[1]Ctr. for Vital Longevity, [2]Univ. of Texas at Dallas, Dallas, TX

Abstract: Cognitive training, particularly executive control and working memory (WM), has been shown to improve both near and far transfer tasks in adults, both healthy and with Mild Cognitive Impairment (Basak et al., 2020). In this study, we examined whether 20 hours of unpredictable WM training (High Executive Control, HEC) on a visuospatial bird-watch game (Smith et al., 2022) induces greater transfer to neural markers of episodic memory in healthy Older Adults when compared to 20 hours of predictable WM training (Low Executive Control, LEC) or when 12 hours of HEC was combined with 8 hours of meditation-based mindfulness training (MBMT+HEC). The Mnemonic Similarity Task (Stark et al., 2007)—a subsequent memory task where Older Adults discriminated between old target, similar lure, and new foil images—was used as the fMRI transfer task. This task yielded encoding-related BOLD activation for subsequently Remembered (target hits + lure hits), Misremembered (targets misidentified as lures + vice versa), and Forgotten images. Memory-sensitive regions were defined for Remember > Forgot and Target Hits > Target Misses in an independent sample of

Young Adults. Age-sensitive regions of interest (ROIs) were also identified from Young > Old and Old contrasts (N_{young}= 24, N_{old}= 64) (Basak et al., submitted 2026). fMRI BOLD mean percent signal change (mPSC) was extracted from baseline and post-training scans in the 43 trained Older Adults. Young > Old ROIs were mainly increased activation of memory-sensitive regions in Young compared to Old. Old ROIs mainly showed reduced deactivation of task-negative regions, e.g. the default mode network. In the Left Lateral Occipital Cortex (L.LOC) & Fusiform Gyrus, a memory-sensitive ROI (Remember > Forgot), Old had reduced mPSC compared to Young for Remembered images. Post-training mPSC was higher in HEC for Remember and Misremember (.214 & .238, respectively) than LEC (.186, .161). MBMT+HEC (.193, .204) showed relatively higher mPSC than LEC but lower than HEC. Importantly, post-training HEC mPSC for Remember matched Young (.206). Similar age-differences favoring Young for Remember and Misremember were observed for encoding specificity of Targets in the Left Temporal Occipital Fusiform Cortex. Post-training mPSC shows that HEC and MBMT+HEC have higher activation than LEC for Remembered and Misremembered images, suggesting generalized increase in this region for visual objects. In the Right LOC & Angular Gyrus, HEC (-.170) showed greater deactivation for Remember than LEC (-.077) and MBMT+HEC (.021). This suggests that greater training time results in more deactivation of this task-negative region, as seen in Young (-.213).

Disclosures: C. Basak: None. **J. Dodgen:** None. **S. Panda:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.19/T8

Topic: C.01. Brain Wellness and Aging

Support: NIH R24 AG065172
NIH K99AG088300-01A1
NIH/NIA P30AG072931
NIH R01 MH135565
NIH R01 NS118440
CZI Collaborative Pairs

Title: Wired for resilience: Inhibitory networks connecting sleep and memory across the aging brain

Authors: *F. RAVEN[1], A. HE[2], A. VAN KAMPEN[1], B. BUNCE[1], A. SHAFI[1], J. KRAVCHENKO[1], J. HELLIN LOPEZ[3], K. MCDONALD[1], C. C. KACZOROWSKI[1], S. J. ATON[1];
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Abstract: Sleep problems and memory loss rank among the most frequent health complaints in older adults and weigh heavily on their quality of life. The leading driver of dementia, Alzheimer's disease (AD), is found in more than 7 million Americans aged 65 and over. Evidence indicates that poor sleep during midlife may elevate the likelihood of developing AD later in life. To test how midlife sleep relates to cognition in old age, we turned to the AD-BXD mouse panel, a genetically heterogeneous population that carries familial AD alleles. Our data show that less sleep in midlife predicts greater memory loss in old age. Among AD-BXD strains prone to cognitive decline, AD pathology is concentrated in thalamic and hippocampal regions — areas that govern sleep regulation and memory processing, respectively — and the degree of this pathology tracks with the severity of cognitive impairment. A selective reduction in the density of somatostatin-expressing (SST^+) interneurons appears in these same regions in vulnerable, though not resilient, AD-BXD strains and predicts how well memory functions in late life. In separate experiments comparing young vs. aged wild-type mice, chemogenetically activating hippocampal SST^+ interneurons reverses age-associated memory impairment in a sex-dependent manner, improving memory in male but not female mice. Collectively, these results point to SST^+ interneurons as a possible cellular bridge linking midlife sleep disruption, network resilience, and the memory decline seen in aging and Alzheimer's disease.

Disclosures: F. Raven: None. **A. He:** None. **A. Van Kampen:** None. **B. Bunce:** None. **A. Shafi:** None. **J. Kravchenko:** None. **J. Hellin Lopez:** None. **K. McDonald:** None. **C.C. Kaczorowski:** None. **S.J. Aton:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.20/T9

Topic: C.01. Brain Wellness and Aging

Support: University of Florida Center for Cognitive Aging and Memory
Office of the Vice President for Research

Title: Aging Related Decline in Social Motivation and Transcriptomic Changes in Prelimbic Cortex and Basolateral Amygdala in Rats

Authors: *T. GOOLD[1], I. RODRIGUEZ-LAUSELL[1], P. NAGENDIRAKUMAR[1], N. DOBRIC[1], B. SETLOW[2], J. L. BIZON[4], F. J. MARTINEZ-RIVERA[3];
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Abstract: Social interaction supports cognitive and physical health in aging, yet social isolation is increasing and is associated with elevated dementia risk and mortality. Although aging research has largely focused on pathology, memory, and cognition, less is known about how aging alters social motivation. We used an operant social self-administration task (SSA) to assess

motivation for social reward in young adult (4 months) and aged (24 months) rats of both sexes. Young females showed the highest responding for social interaction, followed by young males and aged females, whereas aged males showed little motivation to pursue social interaction. In a three-chamber task, all groups displayed social preference, but novelty/familiarity discrimination was only seen in young females and old males. These findings suggest that aged rats may still value social interaction but show reduced motivation to work for it in an operant setting. Rats also self-administered sucrose as an alternative natural reward. All groups responded more for sucrose than for social interaction, although aged rats showed lower overall responding than young. During a conflict phase in which rats chose between sucrose and social interaction, all groups preferred food, suggesting that aging, particularly in males, may reduce social motivation as well as natural reward-guided behavior more broadly. Ongoing single-nucleus RNA sequencing of the basolateral amygdala and prelimbic cortex from naïve young and aged rats revealed age-related cell-type differences, including reductions in inhibitory neuronal and glial populations in aged rats compared to young. Preliminary differential expression analyses identified large-scale transcriptomic differences between age groups. Together, these findings suggest that age-related social motivational decline may link to cell type-specific transcriptional changes in neural circuits involved in reward processing, motivation, and cognitive control.

Disclosures: T. Goold: A. Employment/Salary (full or part-time):; University of Florida. **I. Rodriguez-Lausell:** None. **P. nagendirakumar:** A. Employment/Salary (full or part-time):; University of Florida. **N. Dobric:** None. **B. Setlow:** None. **J.L. Bizon:** None. **F.J. Martinez-Rivera:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.21/T10

Topic: C.01. Brain Wellness and Aging

Support: CIEN Foundation
Queen Sofia Foundation
Spanish Ministry of Science and Innovation (PID2023-153259OB-I00)

Title: The Superager hippocampus: volume preservation across all subfields without differential subfield longitudinal atrophy

Authors: S. LATGÉ TOVAR[1,2], M. GARCIA HUESCAR[1,2,3], C. GASER[4,5,6], *B. A. STRANGE[1,3];
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of Neurology, Jena Univ. Hosp., Jena, Germany; [6]German Ctr. for Mental Hlth. (DZPG), Site Jena-Magdeburg-Halle, Magdeburg, Germany

Abstract: While cognitive decline is often considered a hallmark of aging, superagers retain episodic memory function comparable to that of adults 30 years younger. Characterizing the neural correlates underpinning preserved memory offers an opportunity to understand memory maintenance in older adults and to design future strategies to prevent cognitive decline. A critical question is whether superagers exceptional memory arises from an absence of dementia-related neurodegeneration, or from brain characteristics indicative of a unique phenotype. Neuroimaging studies suggest that superagers show larger hippocampal volume than typical older adults as aging progresses, despite comparable volumes around the age of 75, when their superior memory is already apparent. Recently, Disouky et al. (2026) identified distinct neurobiological signatures within the dentate gyrus (DG) and CA1 subregions of superagers using post-mortem tissue: a higher rate of neurogenesis in DG of superagers as well as molecular signals associated with healthy ageing with intact cognition in CA1. This raises the question of whether resistance to atrophy in hippocampal DG and CA1 account for preserved hippocampal volume, or whether other subfields are also preserved in superaging. We tested this by applying automated hippocampal segmentation on whole-brain T1 scans using FreeSurfer and comparing 18 partitions of hippocampal subfields from superagers (n = 64), age-matched controls (n = 49), and amnestic mild cognitive impairment (aMCI) participants (n = 29) aged 80+ from the Vallecas Project, a longitudinal study with yearly evaluation (median number of follow-up visits: 5.0 (IQR 5.0-6.0) for superagers, 5.0 (4.5-6.0) for age-matched controls, and 5.0 (3.0-7.0) for aMCI). Group comparisons of segmentations from the year in which participants met full criteria for membership to one of these 3 groups revealed a significant group by subfield interaction, with 17 of 18 subfield partitions showing FDR-corrected effect of group (except for parasubiculum), with top 3 reliable effects in DG, CA1 and subiculum within the head region. By contrast, subfield partition volumes did not show a significant group-by-time trajectory interaction: longitudinal atrophy rates across subfields did not differ between groups, suggesting that the reduced overall hippocampal atrophy observed in superagers may not be attributable to selective subregion preservation. Thus, additional mechanisms - beyond DG neurogenesis and CA1 molecular signals - likely underly preserved hippocampal integrity in exceptional cognitive aging.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.22/T11

Topic: C.01. Brain Wellness and Aging

Support: Rutgers University School of Health Professions Dean’s Intramural Grant

Title: Prefrontal 30 Hz tACS Enhances Directed Cortical Connectivity During Dual-Task Performance in Older Adult

Authors: *F. AL-SHARGIE[1], M. GLASSEN[2], S. V. ADAMOVICH[3], S. H. SALEH[4]; [1]Rutgers Univ., Bloomfield, NJ; [2]New Jersey Inst. Of Technol., hillsborough, NJ; [3]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; [4]Rutgers, The State Univ. of New Jersey, Newark, NJ

Abstract: Background: Cognitive reserve may help explain why some older adults maintain cognitive and motor function despite age-related decline. Dual-task (DT) paradigms are commonly used to assess cognitive reserve because they require simultaneous cognitive and motor processing and often reveal deficits not detected during single-task performance. Successful DT control depends on communication among prefrontal, sensorimotor, and default-mode networks. However, the effects of prefrontal 30 Hz transcranial alternating current stimulation (tACS) on directed brain network communication during DT performance remain unclear. This study examined whether 30 Hz tACS enhances cortical network interactions associated with cognitive reserve in older adults. **Methods:** Nine older adults completed a motor-cognitive DT under active 30 Hz tACS and sham stimulation in a crossover design. EEG was recorded from 64 channels and processed using GEDAI-based spatial filtering and sparse Bayesian Champagne source reconstruction. Time series were extracted from 16 cortical regions spanning prefrontal, sensorimotor, and default-mode networks. Directed functional connectivity was estimated across theta, alpha, beta, and gamma bands using Partial Directed Coherence. Directed weighted networks and orthogonal minimum spanning trees identified robust connectivity patterns. Paired t-tests compared stimulation conditions. **Results:** Behavioral performance consistently favored tACS over sham. Accuracy increased from 76.9% to 81.8%, sensitivity from 74.4% to 79.2%, and specificity from 75.9% to 83.2%. Connectivity analyses revealed significantly stronger directed interactions during tACS, particularly in beta and gamma bands. Enhanced connectivity was observed from bilateral dorsolateral prefrontal cortex to primary motor cortex, precuneus, and anterior cingulate cortex, as well as among supplementary motor, sensorimotor, and cingulate regions ($p < 0.05$). Alpha-band findings showed similar but weaker effects, whereas theta-band modulation was limited. Sham exhibited only a few stronger connections involving parietal and premotor regions. **Conclusions:** Prefrontal 30 Hz tACS enhanced task-related network communication during DT performance, strengthening connectivity among prefrontal, sensorimotor, and cingulate regions involved in cognitive control and motor integration. Although behavioral improvements were not statistically significant, consistent performance gains and widespread connectivity enhancements suggest that tACS may support neural mechanisms underlying cognitive reserve in aging.

Disclosures: F. Al-Shargie: None. **M. Glassen:** None. **S.V. Adamovich:** None. **S.H. Saleh:** None.

Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

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Program #/Poster #: PSTR047.23/T12

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA 1R01AG079345

Title: Behavioral Repetition Priming and Working Memory in Healthy Aging

Authors: *D. K. PIMENTEL-HURLBURT[1], Z. JUNG[2], M. HE[3], P. L. PURDON[4];
[1]Dept. of Anesthesiology, Perioperative and Pain Med., Stanford Univ., Stanford, CA; [2]Stanford Univ., Palo Alto, CA, ; [3]Psychology, Stanford Univ., Palo Alto, CA; [4]Stanford Univ. Sch. of Med., Palo Alto, CA

Abstract: The ability to maintain goal relevant information while ignoring irrelevant information is a critical component of working memory and cognitive control. Previous research has demonstrated repeated exposure to stimuli produces repetition priming, reflected by faster behavioral responses and reduced neural activity associated with familiarity. Studies using repeated target and distractor stimuli suggest familiarity and behavioral relevance is supported by distinct neural mechanisms. Frontal brain regions appear to track task relevance and working memory goals, whereas posterior visual regions reflect repetition related familiarity. Further aging research suggest repetition priming is largely preserved in older adults despite age related changes in the neural systems.This present study looks to examine repetition priming in healthy older adults ages 65-90 years old using the Bluegrass Memory Paradigm, a working memory task in which participants maintain target images while making recognition judgments about repeatedly presented target and distractor stimuli. Reaction time and accuracy will be examined across the first, second, and third presentations of repeated stimuli. Repetition priming will be assessed as reductions in reaction timing across repeated exposure, and priming effects will be compared across target and distractor conditions to determine whether behavioral relevance influences the magnitude of repetition priming.To examine individual differences in cognitive function, neuropsychological measures of working memory will be analyzed. Repetition priming scores taken from target and distractor conditions will be correlated with working memory performance to determine whether the magnitude or repetition related facilitation is associated with cognitive ability. Because target processing requires more active maintenance of goal related information, working memory performance may show a stronger relationship with target related priming rather than with distractor related priming.We hypothesize participants will demonstrate significant repetition priming, evident by faster reaction time across repeated presentations. Consistent with prior findings, we predict priming effects will differ between targets and distractors, with distractor stimuli showing larger repetition related facilitation than target stimuli. We further predict individual differences in working memory performance will be associated with priming magnitude, particularly for target stimuli. These findings will contribute to understanding how familiarity, behavioral relevance, and working memory interact during cognitive aging.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR047.24/T13

Topic: C.01. Brain Wellness and Aging

Support: NIH T32 AG044402

Title: Rope-pulling system to study sensorimotor integration using upper-extremity kinematics and distance estimation in aging and clinical populations

Authors: *A. VISHWANATH[1], B. FARLEY[4], S. J. SHERMAN[2], C. A. BARNES[3], S. L. COWEN[1], A. D. EKSTROM[1];
[1]Psychology, [2]Neurol., [3]Evelyn F. McKnight Brain Inst., Univ. of Arizona, Tucson, AZ;
[4]Parkinson's Wellness and Recovery, Tucson, AZ

Abstract: Everyday tasks, such as picking up a coffee cup or tying shoelaces, require coordinated upper-limb reaching, grasping, and pulling movements. These tasks demand effective integration of sensory information, such as vision and proprioception, with the execution of motor commands. Deterioration in sensorimotor integration, either during healthy aging or with cognitive/motor disorders, can increase inaccuracies in motor judgements that adversely affect the quality of life. Currently, there are limited bimanual and functional goal-directed tasks for assessing sensorimotor integration that target upper-extremities. Furthermore, most existing tasks do not assess fine motor control or inter-limb coordination. To address this, we developed a rope-pulling task inspired by established string-pulling behaviors used in animal models. The task allows for tracking upper-limb bimanual motor function and coordination (i.e., alternating reach, grasp, and pull movements) using a “continuous loop” of rope. This task, in contrast to tasks that focus on gait, can be used in walking-impaired populations. We used machine vision (DeepLabCut) to measure precise sub-second kinematics of hand movement such as inter-limb coordination (phase and timing relationships), gross motor (reaching and pulling, overall movement speed/amplitude), and fine motor (grasping) movements during rope pulling. Furthermore, we developed a variant of this task to assess the capacity of subjects to estimate and reproduce distances (lengths of rope) pulled given evidence that distance estimation is disrupted in aging, Alzheimer’s disease, and Parkinson’s disease. For evaluating distance reproduction, participants, in a given trial, are asked to remember a target distance of rope and reproduce the distance from memory. The relationship between motor kinematics and distance estimation will be assessed using a computational model to predict how distance perception alters motor control. Thus, this rope-pulling task is novel in its capacity to seamlessly incorporate cognitive goal-directed behaviors with complex functional movements.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

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Program #/Poster #: PSTR047.25/T14

Topic: C.01. Brain Wellness and Aging

Support: NIH RF1AG073210
NIH RF1AG074992

Title: Multimodal PET Assessment of Deep White Matter Metabolism in Healthy Older Adults

Authors: *R. RENEAU[1], N. METCALF[2], T. BLAZEY[2], J. LEE[2], A. SNYDER[2], A. G. VLASSENKO[2], M. GOYAL[2];
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Abstract: Background: White matter is often treated as a PET reference or normalization region. Yet, its biological properties, age-related variability, and sensitivity to partial-volume effects remain uncertain. We developed a multimodal PET framework to estimate deep white matter metabolism while limiting grey matter spill-in and ventricular contamination, and examined white matter signal changes with aging in cognitively healthy older adults. Exclusion criteria included a CDR greater than zero, a moderate or severe white matter disease burden (Fazekas score), and, for participants above age 55, amyloid-positivity through testing. Methods: [18F] FDG, [15O] H2O, [15O] CO, and [15O] O2 PET data were collected on Siemens Biograph Vision PET/CT scanner. These tracers measure glucose consumption, cerebral blood flow (CBF), cerebral blood volume, and enable computation of the oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO2). Subject-specific white matter masks were generated from FreeSurfer tissue segmentation and then subsequent distance from grey matter and distance from ventricles maps were created. Deep white matter was defined using grey matter partial-volume effect simulations, non-parametric flexible modeling, and distance-from-grey-matter (7.5 mm-10 mm)-and-ventricle (>5mm) criteria. For each modality, grey matter and deep white matter mean values were extracted, and grey-to-white matter ratios were computed. Age associations were tested with sex-adjusted models. Results: The pipeline consistently identified a deep white matter region across participants. Across FDG, CBF, CBV, rOEF, and rCMRO2, grey matter and white matter showed age-related patterns. Specifically, non-partial-volume corrected analyses suggested that FDG, CBF, and rCMRO2 grey-to-white matter ratios decreased with advancing age. Ongoing analyses will incorporate partial-volume correction to account for cortical thinning and kinetic modeling to quantitatively evaluate white matter metabolism. Conclusion: This project establishes a subject-specific, distance-based approach for measuring deep white matter PET data across metabolic modalities. The findings carry implications for PET reference-region selection and interpretation of white matter signals in aging and neuropsychiatric and neurodegenerative diseases. Ongoing analyses investigate grey-to-white matter ratios of brain metabolism and blood flow as a function of age.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

Location: WCC Halls A-C

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Program #/Poster #: PSTR047.26/T15

Topic: C.01. Brain Wellness and Aging

Support: Conte Center P50MH132642

Title: Functional Organization of Thalamocortical Connectivity in Healthy Aging

Authors: *D. KING, X. LIU, M. ARCARO;
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Abstract: Healthy cognitive aging is variable, even among adults without neurological disease. This variability is unlikely to reflect focal deterioration alone and may instead arise from changes in the large-scale networks that coordinate communication across the brain. The thalamus is well positioned to contribute to this systems-level change. Through dense, topographically organized connectivity with sensorimotor, limbic, and association cortices, it helps regulate distributed cortical activity and supports multiple cognitive domains. Recent work shows that thalamocortical connectivity forms continuous functional topographies that embed cortical network structure within the thalamus. Aging may therefore alter this organization in multiple ways, including global degradation, network-specific reweighting, loss of topographic structure, or increasingly individualized connectivity profiles.Using resting-state fMRI from the cross-sectional Cambridge Centre for Aging and Neuroscience dataset (18-88; N = 650), we characterized thalamocortical coupling across the healthy adult lifespan using functional connectivity fingerprinting (fpFC), which describes each thalamic voxel by its distributed pattern of cortical coactivation. Comparing the fpFC profile of each participant revealed that thalamocortical coactivation structure shifts systematically with age. While younger adults shared a similar global structure, older adult profiles became increasingly heterogenous, diverging from both younger adults and one another. To identify which features of the cortical map changed with age, we decomposed fpFC into principal spatial gradients. The strongest gradient ran from primary sensory and motor cortex to higher-order association cortex, mirroring the canonical sensorimotor-association (S-A) axis observed across cortex. With age, however, the S-A axis weakened relative to a second gradient separating modulatory from representational cortex, which remained more stable across the lifespan. This shift was driven by visual and motor regions, suggesting that age-related changes at the sensorimotor pole were most responsible for the diminished influence. Together, these findings show that thalamocortical functional topography does not degrade uniformly with age but reorganizes in a structured and increasingly individualized manner along existing cortical gradients. This pattern may reflect person-specific differences in sensorimotor experience and cognitive vulnerability, offering insight into how changes in the functional map linking thalamus and cortex may contribute to variability in healthy cognitive aging.

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Poster

PSTR047: Behavior and Cognitive Disorders Across Aging

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Topic: C.01. Brain Wellness and Aging

Support: Tow Research and Mentoring Summer Program
Tow Faculty and Research Creativity Grant #92301-00 20
Tow Research and Mentoring Grant Fall 2026

Title: Neighborhood Socioeconomic Deprivation, Racial Disparities and Healthcare Utilization in Neurological and Neurodegenerative Disease Mortality: A National Analysis

Authors: A. MALDONADO, *S. SAMADDAR;
Biology/Neuroscience, Brooklyn Col., Brooklyn, NY

Abstract: Background: Neurodegenerative and cognitive disorders represent an escalating public health burden in the United States, marked by progressive disability, high hospitalization rates, and substantial healthcare expenditure. Stark racial and ethnic disparities in neurological disease incidence, diagnosis, treatment access, and outcomes remain well-documented yet poorly addressed, with minoritized populations less likely to receive timely diagnosis and more likely to experience aggressive end-of-life intervention and higher hospitalization rates. **Methods:** County-level age-adjusted mortality rates for traumatic brain injury (TBI) and Parkinson's disease (PD) from CDC WONDER (2015-2020) were linked with standardized Area Deprivation Index (ADI) scores to evaluate associations between structural socioeconomic disadvantage and neurological mortality. Univariate, stratified, interaction, and multivariable linear regression models assessed relationships across demographic and geographic subgroups. Subsequently, inpatient data from HCUP (2016-2023) will be analyzed to characterize hospitalization trends, racial disparities, payer differences, and resource utilization, length of stay, total hospitalization charges, complication rates, stratified by disorder type, age group, sex, and calendar year across neurodegenerative and cognitive disorders. Additionally, we intend to identify independent predictors of in-hospital mortality using multivariable regression modeling, accounting for patient demographics and comorbidity burden. **Results:** Higher ADI independently predicted increased TBI mortality before and after adjustment, with stronger effects among males and in micropolitan counties. For PD, ADI associations were attenuated after multivariable adjustment, though significant urbanization-dependent interaction effects persisted in less-urban regions. PD mortality rose substantially between 2015 and 2020, with urbanization emerging as a dominant predictor. Inpatient data analyses from the HCUP database will help us understand the interrelationships between these socioeconomic disparities and treatment outcomes. **Conclusions:** Structural socioeconomic disadvantage and racial inequity shape neurological mortality through disease-specific pathways involving injury exposure, trauma system access,

and continuity of specialty care. Integrating deprivation measures into neurological health planning may identify vulnerable communities and guide interventions to reduce mortality disparities.

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Poster

PSTR048: Neural Mechanisms of Aging

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Program #/Poster #: PSTR048.01/T17

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG075000

Title: Higher cost, but adaptive: age-related compensation in locus coeruleus-salience network coupling during distraction

Authors: *Y.-Y. CHEN[1], E. SEAGO[2], B. KATZ[2], T.-H. LEE[1];
[1]Psychology, [2]Human Develop., Virginia Tech., Blacksburg, VA

Abstract: The locus coeruleus (LC) is central to noradrenergic modulation of attention, yet how LC-cortical coupling dynamically adapts to sensory demands and aging remains unclear. Using task-based fMRI with functional and effective connectivity, we examined LC-cortical network coupling during selective attention in 108 adults, divided into a younger (YA; $n = 54$; 18-40 years) and older (OA; $n = 54$; 55-75 years) groups. Participants performed a place discrimination task, judging a target scene (house vs. building) while either ignoring an overlapping face distractor (dual) or not (single). Distraction reliably slowed responses and reduced accuracy ($ps < .001$) in both groups, confirming an effective manipulation. Older adults maintained accuracy well above chance under distraction, although they showed disproportionately larger costs (reaction-time interference 37 vs. 16 ms; Condition × Group: $F = 18.57$, $p < .001$).
Functional connectivity analyses showed that weaker sensory-perceptual responses in the parahippocampal place area (PPA) during distraction (dual > single) were associated with stronger LC coupling to the anterior cingulate cortex (ACC) and prefrontal control regions (dlPFC). This inverse relationship in the LC-ACC pathway was amplified in OA (PPA × Age Group: $B = 0.371$, $p = .028$), whereas no comparable age interaction emerged for LC-dlPFC ($B = -0.421$, $p = .118$). The LC-ACC interaction suggests a compensatory upregulation of neuromodulatory control: that is, LC-cortical coupling may help maintain performance under distraction when sensory-perceptual processing is insufficient.
We next asked whether this neural architecture (among PPA, LC, ACC, and dlPFC) is preserved with aging, and whether the compensation reflects a top-down process (LC amplifying frontal regions that modulate PPA) or a bottom-up process (PPA driving LC and frontal regions). Dynamic causal modelling confirmed that the top-down causal architecture of LC-cortical networks was preserved across the adult lifespan: family-level Bayesian model selection strongly

favored a top-down control architecture (exceedance probability = 0.983), and parametric Bayes analysis revealed no reliable age-related differences in intrinsic or task-dependent connectivity. Individual differences in attentional performance were selectively predicted by the strength of top-down feedback from attention and control regions to sensory cortex (r = -.205, p = .038), not by LC modulatory drive to control regions (r = -.122, p = .219). Together, these findings indicate that age-related differences in attentional control reflect adaptive reweighting within a preserved network architecture.

Disclosures: Y. Chen: None. **E. Seago:** None. **B. Katz:** None. **T. Lee:** None.

Poster

PSTR048: Neural Mechanisms of Aging

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Program #/Poster #: PSTR048.02/T18

Topic: C.01. Brain Wellness and Aging

Support: Virginia Commonwealth Alzheimer and Related Disease Award, 2023

Title: What we've been (Ver)missing: Activation of the cerebellar vermis in a spatial memory task

Authors: G. LUTZ, ***R. P. HABERMAN**;
Mary Baldwin Univ., Staunton, VA

Abstract: Despite extensive research, the full breadth of mechanisms underlying memory impairment in aging and neurodegenerative disease remains obscure, serving as a major barrier to therapeutic development. The cerebellum, conspicuously limited in this literature, is potentially one of these unknown memory contributors. Traditionally thought to serve only a motor function, recent studies have redefined its role, highlighting its involvement in higher cognitive processes including memory. Further exploration of the cerebellum's cognitive role in human studies has identified the cerebellar vermis, the structure connecting the bilateral cerebellar hemispheres, as showing the most consistent activation across cognitive measures and strong associations with multiple neurodegenerative disorders. Since spatial memory loss is a common component of aging and an early symptom of Alzheimer dementia, our study aimed to directly address the role of the cerebellar vermis in spatial memory using an established rat model which tightly controls for confounding effects of motor activity. Memory was assessed through a cue mismatch task, in which rats, acclimated to a stable environment over 10 days, were exposed to a misalignment of local and distal cues on the final test day. This cue mismatch-induced neural activation was determined by c-Fos immunohistochemistry of the vermis and the hippocampus (as a control region). In the cerebellar analysis, rats exposed to the cue mismatch exhibited significantly greater vermal activation than either homecage control or a no mismatch control group that was exposed to the acclimated cue configuration on test day and exhibited similar physical activity levels as the mismatch group. Behaviorally, the cue mismatch resulted

in increased head scans, a marker of spatial memory engagement, relative to the no mismatch controls. However, neither physical activity, measured by number of laps traversed nor head scan count correlated with vermis activation, implying that the cerebellar response reflected a distinct, non-motor, non-hippocampal response. These findings support emerging models of cerebellar involvement in spatial memory, possibly in sequencing and error detection, and position the vermis as a meaningful contributor to spatial memory independent of locomotor or hippocampal activity.

Disclosures: G. Lutz: None. **R.P. Haberman:** None.

Poster

PSTR048: Neural Mechanisms of Aging

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Topic: C.01. Brain Wellness and Aging

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Title: Associations among handgrip asymmetry, striatal dopamine synthesis capacity, and longitudinal cognition in aging

Authors: *P. CAO[1,2], T. M. MORIN[1,2], K. XIKES[1], A. J. KINNEY[1], J. M. HOOKER[2], A. S. BERRY[1];
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Abstract: Handgrip strength (HGS) is a non-invasive indicator of vitality and previous studies have proposed that shared age-related neural changes mediate the HGS-cognition relationship observed in older adults. Beyond absolute HGS, recent research has found that older adults with asymmetric HGS show worse cognitive function, suggesting that HGS asymmetry (HGS-A) may also reflect neural mechanisms associated with cognitive decline. Age-related changes to striatal dopamine have been implicated in both motor and cognitive performance with an upregulation in dopamine synthesis capacity posited to reflect suboptimal dopaminergic function. Thus, the aging striatal dopamine system represents a candidate neurochemical factor underlying HGS-A. We examined the relationships among striatal dopamine synthesis capacity as measured by [18F]fluoro-l-m-tyrosine ([18F]FMT) MR-PET scanning, HGS-A, and longitudinal working memory as assessed by the digit span test in healthy older adults (n = 56, mean age = 71.59, 34 female). Participants underwent bilateral HGS assessment and percent HGS-A was calculated with the following formula: [(stronger HGS − weaker HGS) / stronger HGS] × 100. HGS-A showed a logarithmic relationship with [18F]FMT in left dorsal putamen (DPU; t = 2.65, p = .01) such that there was a positive association between left DPU [18F]FMT and HGS-A among

individuals with symmetric HGS (HGS-A less than 15%; t = 3.32, p = .002) but not in individuals with asymmetric HGS (HGS-A of at least 15%; t = 1.04, p = .32). Additionally, we found a significant interaction effect of Time x left DPU [18F]FMT on working memory such that greater dopamine synthesis capacity predicted working memory decline (t = -2.64, p = .01). Complementary analyses of longitudinal working memory in a larger sample (n = 171, mean age = 70.66, 97 female) found that asymmetric HGS at baseline was associated with greater working memory decline (W = 2933, p = .04). Though correlational, when taken together our analyses suggest that striatal dopamine influences HGS-A and cognition in old age, with increased dopamine synthesis capacity serving as an indicator of nonoptimal dopamine function.

Disclosures: P. Cao: None. **T.M. Morin:** F. Consulting Fees (e.g., advisory boards); T. M. Morin has received consulting fees from Rocket Science Health. **K. Xikes:** None. **A.J. Kinney:** None. **J.M. Hooker:** A. Employment/Salary (full or part-time):; J. M. Hooker is co-founder of and equity holder in Eikonizo Therapeutics and Sensorium Therapeutics, where he also serves as CEO. F. Consulting Fees (e.g., advisory boards); J. M. Hooker is currently an advisor to Rocket Science Health, Human Health, Delix Therapeutics, and Psy Therapeutics. **A.S. Berry:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.04/T20

Topic: C.01. Brain Wellness and Aging

Title: Postsynaptic TAK1 signaling is required for the maintenance of excitatory synapses and cognitive function during aging

Authors: *K.-W. HE;
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Abstract: Transforming growth factor β-activated kinase 1 (TAK1/MAP3K7) is widely recognized for its roles in immune and stress signaling, but its physiological function in the adult brain remains incompletely understood. Here we investigated the role of neuronal TAK1 in synaptic function and cognition. Reduction of TAK1 in forebrain excitatory neurons impaired hippocampus-dependent memory and was associated with deficits in excitatory synaptic transmission, synaptic plasticity, and dendritic spine maintenance. Pharmacological inhibition of TAK1 produced similar synaptic alterations, supporting a requirement for TAK1 kinase activity in the regulation of excitatory synapses. Biochemical and proteomic analyses identified TAK1 as a component of postsynaptic signaling networks and revealed broad changes in synaptic protein phosphorylation following TAK1 reduction. Functional studies further demonstrated that TAK1 signaling contributes to the maintenance of dendritic spine stability and synaptic calcium dynamics through downstream synaptic effectors.Importantly, synaptic TAK1 expression was reduced in the aged hippocampus. Enhancing neuronal TAK1 signaling in aged mice increased dendritic spine density, improved hippocampal synaptic function, and enhanced memory

performance. Together, these findings identify TAK1 as a previously unrecognized regulator of postsynaptic integrity and cognitive function. The results suggest that age-related disruption of synaptic TAK1 signaling may contribute to hippocampal dysfunction during aging and highlight this pathway as a potential target for preserving synaptic health and cognitive resilience in the aging brain.

Disclosures: K. He: None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.05/T21

Topic: C.01. Brain Wellness and Aging

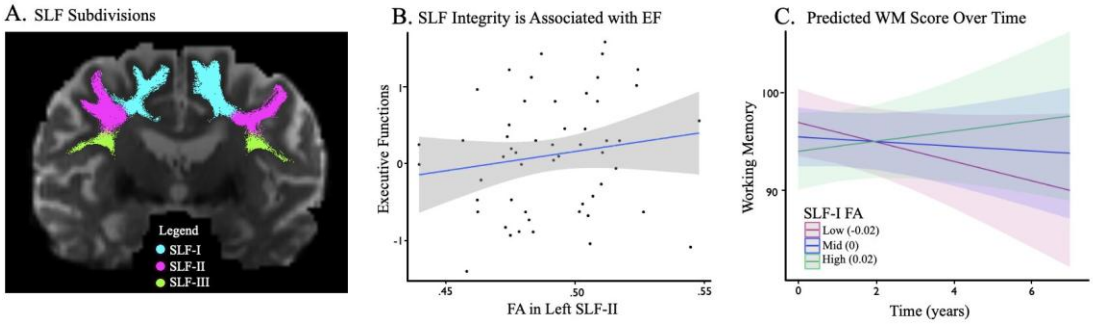
Support: This work was supported by the SUNY Stony Brook Research Foundation.
Data, methods used, and/or research reported in this presentation were provided in whole or in part by the Aging Adult Vulnerability and Resiliency in the Aging Adult Brain Connectome (AABC) project (U19AG073585).
Additionally the Human Connectome Project in Aging (HCP-A, U01AG052564) funded by the National Institute of Aging of the National Institutes of Health. HCP-A was further supported by funds provided by the McDonnell Center for Neuroscience at Washington University in St. Louis.

Title: Structural integrity of the superior longitudinal fasciculus subcompartments and cognitive change in older adults

Authors: *K. SOLIS, K. FARBER, X. CHEN, H.-C. LEUNG;
Integrative Neurosci. Program, Dept. of Psychology, Stony Brook University, NY 11794-2500, Stony Brook Univ., Stony Brook, NY

Abstract: The superior longitudinal fasciculus (SLF) is one of the largest white matter tracts in the human brain, connecting frontal and parietal regions. The integrity of SLF has been implicated in cognitive outcomes. Age-related alteration in white matter integrity may contribute to cognitive decline, however longitudinal relationships between SLF and cognitive changes remain understudied. This study examines whether baseline SLF integrity is related to cognitive performance and longitudinal cognitive trajectories in healthy older adults. Diffusion-weighted images were collected across multiple sites using harmonized 3T MRI acquisition protocols as part of the Lifespan Human Connectome Project Aging Study. Preliminary analyses are conducted on a subset of participants (N = 53; Age = 72.3 ± 13.6 years; Female = 55%) using constrained spherical deconvolution modeling and probabilistic tractography to reconstruct the three SLF subdivisions in each hemisphere (Fig. 1A). Fractional anisotropy (FA) is used to index SLF integrity. Cognitive measures include executive function and working memory tasks from the NIH Toolbox. Linear-mixed effects models are used to examine structure-cognitive change

associations across time while controlling for age and sex. Preliminary results show higher baseline SLF-II FA is associated with better executive function performance across participants (Fig. 1B). Further, a significant FA x Time interaction is found, with higher baseline FA of SLF-I being associated with better maintained working memory over time (Fig. 1C). Our preliminary findings support that the integrity of specific SLF subdivisions is related to executive function performance across older participants, and that baseline SLF integrity may predict working memory decline in aging.



1A: SLF subdivisions in left and right hemisphere shown in a coronal section. Blue refers to SLF-I, pink refers to SLF-II, and green refers to SLF-III.

1B: At baseline, the integrity of SLF-II in the left hemisphere is positively associated with executive function (EF) performance across participants.

1C: Higher baseline FA of SLF-I is associated with better maintained working memory (WM) performance over time.

Disclosures: K. Solis: None. **K. Farber:** None. **X. Chen:** None. **H. Leung:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.06/T22

Topic: C.01. Brain Wellness and Aging

Support: R01AG038465

Title: Age-Related Differences in the Predictive Utility of Structural Brain Measures for Fluid and Crystallized Cognition

Authors: M. CHA, M. KURKURE, A. FRANTZEN, Y. STERN, *C. G. HABECK; Columbia Univ., New York, NY

Abstract: Fluid and crystallized cognition show distinct aging trajectories, with fluid abilities declining while crystallized knowledge remains relatively preserved. Understanding how brain structure maps onto these trajectories is crucial for distinguishing normal from pathological aging. We used out-of-sample prediction to evaluate multimodal structural brain measures as predictors of fluid cognition, assessed with reasoning tasks, and crystallized cognition, assessed

with vocabulary tasks, in cognitively normal adults. The age range was 19 to 83 years. Final analytic samples comprised 556 participants for fluid cognition and 550 for crystallized cognition. In these cross-sectional data, younger and older groups were split at the median age of 58 years to examine age-related differences in brain-cognition prediction. Predictors of cognition included cortical thickness, intracranial volume-adjusted cortical volume in 68 surface regions, and deep gray matter volume in 14 regions, sex, and years of education, totaling 152 features. Preliminary held-out comparisons showed that regularized approaches outperformed ordinary regression, and Elastic Net with leave-one-out cross-validation was selected for its robust performance and ability to handle highly correlated predictors. Separate models were fit for younger and older adults. Prediction accuracy was evaluated across 1,000 repeated held-out train-test splits (train n = 214, test n = 53), and age-group differences in the held-out prediction success were assessed using permutation testing. Structural brain measures predicted fluid cognition substantially better in younger than older adults (median r^2 = .229 vs .043; Δr^2 = .166, p = .020), whereas prediction of crystallized cognition was similar across age groups (median r^2 = .252 vs .210; Δr^2 = .062, p = .406). Younger-adult models selected more predictors for both domains (fluid: 36 vs 10.5; crystallized: 32 vs 22). These findings demonstrate that the predictive utility of structural brain measures differs across cognitive domains and age groups, underscoring the importance of age-sensitive approaches to brain-cognition prediction. The marked reduction in prediction utility for fluid cognition in older adults suggests that preserved cognitive function in later life may rely less on structural brain measures and more on compensatory mechanisms and factors not captured by the present study.

Disclosures: M. Cha: None. **M. Kurkure:** None. **A. Frantzen:** None. **Y. Stern:** None. **C.G. Habeck:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.07/T23

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG092219

Title: Within-subject fMRI framework for longitudinal lesion studies in mice: Probing hub vs. non-hub effects on large-scale brain network organization

Authors: *A. VASHISHT[1], T. YOUNG[1], G. VILL[1], M. Y. CHAN[2], E. WINTER-NELSON[2,4], G. S. WIG[2,3], I. KAHN[1];
[1]Columbia Univ. Zuckerman Inst., New York, NY; [2]Ctr. for Vital Longevity, [3]Psychology, Univ. of Texas, Dallas, TX; [4]Columbia Univ. Irving Med. Ctr., New York, NY

Abstract: System segregation, a measure of the modular organization of large-scale brain networks, declines with age in humans and mice (Winter-Nelson et al., PNAS, 2026). Whether

these declines are linked to deterioration of specific nodes or edges is unclear. The mouse model offers an experimental platform to test specific hypotheses and drivers of age-related brain network decline. For example, it is possible that age-related brain network decline is due to degradation of brain network hubs. However, evaluating whether highly connected hub regions vs. non-hub regions differentially drive network decline has been difficult to test longitudinally, owing to limited surgical access following prior MRI headpost implantation. We present a novel stereotaxic method that overcomes this barrier, enabling precise ROI-targeted lesions following headpost implantation, and therefore facilitating within-subject tracking of mouse brain networks before and after lesion. Critically, we used structural MRI to quantify lesion extent in vivo, overcoming the processing artifacts inherent to conventional histological verification methods. Using this approach, we investigated how focal lesions to hub vs. non-hub regions alter functional connectivity and cognition across a broad segment of adulthood. All male and female C57BL/6 mice (n=20 hub lesions, n=20 non-hub lesions, n=20 non-lesioned) underwent resting-state fMRI and behavioral testing (motion sequencing, open-field and novel object recognition) at 3 and 9 months. Following the headpost-implantation surgery and a 3-mo baseline scan, mice received stereotaxic aspiration lesions to either a brain network hub (retrosplenial cortex) or non-hub (gustatory cortex) region (or no lesion, in the non-lesioned control group). Longitudinal imaging analyses quantified changes in whole brain network organization and the effects of focal lesions on system segregation relative to pre-lesion baseline, with particular emphasis on differences between impacts of hub and non-hub lesions. Behavioral assessments characterized the impact of hub and non-hub lesions on recognition memory and cognitive performance. This work establishes a methodological framework for longitudinal lesion studies in rodents, and examines the relationship between network centrality and trajectories of brain network changes following focal damage, with implications for understanding how focal pathology initiates broader network failure in aging.

Disclosures: A. Vashisht: None. **T. Young:** None. **G. Vill:** None. **M.Y. Chan:** None. **E. Winter-Nelson:** None. **G.S. Wig:** None. **I. Kahn:** None.

Poster

PSTR048: Neural Mechanisms of Aging

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.08/T24

Topic: C.01. Brain Wellness and Aging

Support: R01AG076030
T32NS082145

Title: Follicular depletion drives hippocampal-dopamine circuit dysfunction during reproductive aging

Authors: *S. M. PEREZ[1], A. M. BOLEY[2], K. LILLY[3], D. J. LODGE[4];
[2]Pharmacol., [1]UT Hlth. San Antonio, San Antonio, TX; [3]UT Hlth. San Antonio, SAN ANTONIO, TX; [4]UTHSCSA, San Antonio, TX

Abstract: The transition to menopause represents a period of increased psychiatric vulnerability, including the onset and exacerbation of psychotic disorders. Although rodent models have identified hippocampal hyperactivity as a potential mechanism underlying menopause-associated behavioral disruption, whether this circuit dysfunction persists when follicular depletion occurs during reproductive aging remains unclear. We utilized an aged (11-12 months) rat model of 4-vinylcyclohexene diepoxide (VCD)-induced follicular depletion to mimic menopause in a translationally relevant, aged neurobiological context. Following ovarian follicle depletion, aged VCD-treated rats displayed a robust increase in VTA dopamine neuron population activity. Local inactivation of the vHipp with TTX completely reversed this hyperactivity, demonstrating that aberrant hippocampal output is necessary for menopause-associated dopamine system dysregulation. These circuit alterations were accompanied by deficits in recognition memory and enhanced psychostimulant sensitivity, consistent with behavioral consequences of hippocampal-dopamine dysregulation. Together, these findings demonstrate that vHipp-driven dopaminergic dysfunction is a conserved neurobiological consequence of follicular depletion that persists during reproductive aging. Furthermore, the similarity between juvenile and aged VCD phenotypes supports the juvenile VCD model as a reliable surrogate for mechanistic studies, while confirming that the same core circuit vulnerability is present when follicular depletion occurs later in life. Ultimately, these data identify the hippocampus as a critical upstream driver of menopause-related psychiatric vulnerability and highlight hippocampal-VTA regulation as a candidate target for circuit-based interventions.

Disclosures: S.M. Perez: None. **A.M. Boley:** None. **K. Lilly:** None. **D.J. Lodge:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.09/T25

Topic: C.01. Brain Wellness and Aging

Support: NIH NCATS Grant K12TR004555

Title: Individualized patterns of cortico-hippocampal connectivity and microstructural degeneration across aging and cognitive decline

Authors: *E. HECHAVARRIA, J. MILLER;
Psychology, Univ. of Miami, Coral Gables, FL

Abstract: Aging-related cognitive decline is a substantial public health concern, yet identifying neural mechanisms for this decline remains elusive. Previous research shows that resting state functional connectivity (RSFC) between the hippocampus and cortex decreases significantly

with aging and memory decline. However, to interrogate brain aging mechanisms and provide clinical utility, individualized profiles of cortical circuit (dys-)function are needed. Here, we used a precision neuroimaging approach to link hippocampal RSFC, cortical microstructure, and cognition in two lifespan, high-resolution MRI datasets (Jansen et al., 2024: n=295, 18-80yo, Babayan et al., 2019: n=227, 20-77yo). For each older individual (>=59yo), we calculated a hippocampal RSFC "variant" map showing their divergent patterns of RSFC versus a normative average of younger adults. From these individual connectivity "variant" maps, we then divided older individuals into subgroups of altered cortico-hippocampal RSFC. For example, anterior hippocampal connectivity in older adults showed three distinct subgroups with reduced connectivity to anterior temporal, somatomotor, and medial frontal cortices. We then analyzed cortical microstructure and profiles of cognitive functioning between the connectivity-defined aging subgroups. We created multivariate, composite cognitive measures from a suite of neuropsychological test scores (e.g., CVLT, TMT) via principal component analysis. We found that these cognitive profiles significantly differed between subgroups of older individuals defined from cortico-hippocampal RSFC. For instance, anterior hippocampal connectivity subgroups showed significant variation in executive functioning. Older individuals with reduced hippocampal RSFC in the medial frontal cortex also showed decreased cortical myelination compared to other older individuals and younger adults. These changes were driven by decreases in iron- and myelin-sensitive MRI markers (quantitative T2* and R1) in superficial cortical layers, which receive memory-related inputs from the hippocampus. These results critically link individualized hippocampal functional connectivity changes to anatomical brain changes and cognitive outcomes.

Disclosures: E. Hechavarria: None. **J. Miller:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.10/T26

Topic: C.01. Brain Wellness and Aging

Support: Japan Society for Promotion of Science (JSPS) Research Fellowship for Young Scientists [23KJ0194]
the Cooperative Research Project Program of Joint Usage/Research Center at the Institute of Development, Aging and Cancer, Tohoku University
MRI Research Challenging and Collaborative Research Grant, Center of Cognitive Neuroscience Application (CogNAC), Tohoku University

Title: Neural substrates of speech act recognition in younger and older Japanese adults

Authors: *L. TAN[1], T. IWABUCHI[2], M. KASAI[5,3], S. KATO[3], M. SUGIURA[4], S. KIYAMA[3,4];

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Abstract: Wisdom extends beyond cognitive efficiency, involving context-sensitive understanding of human actions in complex situations (Baltes & Staudinger, 2000). Yet aging research has focused largely on cognitive decline, leaving unclear how wisdom-related social-pragmatic understanding differs between younger and older adults. Speech act recognition provides a window into this issue: it requires listeners to infer the action a speaker intends to perform through an utterance. The present study examined its neural substrates in younger and older Japanese adults using functional magnetic resonance imaging (fMRI). In a recognition task, participants first viewed a probe word, followed by a context and a target utterance forming a short dialogue. During presentation of the target utterance, they judged whether the communicative intention expressed by the target utterance matched the intention represented by the probe word. We compared speech act (SpAct) trials in which the speech act represented by the probe word was expressed in the target utterance (e.g., probe word: “accept”; target utterance: “If I may, I would be happy to take it on.”) with non-speech act (non-SpAct) trials in which it was not realized, resulting in a mismatch between the probe-word speech act and the intention expressed by the target utterance (e.g., probe word: “assert”; target utterance: “If that’s acceptable, I’d like to let the trainee handle it”). We analyzed data from 25 younger adults (10 females; age: $M = 21.44$, $SD = 1.71$) and 32 older adults (12 females; age: $M = 70.41$, $SD = 3.50$), all native Japanese speakers, using a whole-brain flexible factorial model. The model revealed greater activation for non-SpAct than SpAct trials in the left putamen, precuneus, superior frontal gyrus, anterior cingulate cortex, anterior insula, and planum temporale. We also found that younger adults had a larger non-SpAct versus SpAct activation difference than older adults in the right middle frontal gyrus. All reported clusters met a voxel-level threshold of $p < .001$ (uncorrected) and a cluster-level threshold of $p < .05$ corrected for family-wise error. The right middle frontal gyrus is linked to multiple functions, including prediction-error-related processing. Greater activation in younger adults may reflect stronger probe-cued prediction: in non-SpAct trials, the target utterance violated the intention predicted from the probe word. Older adults may instead have relied more on the utterance and broader context, experiencing less incongruence between the probe-cued and expressed intentions.

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Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.11/T27

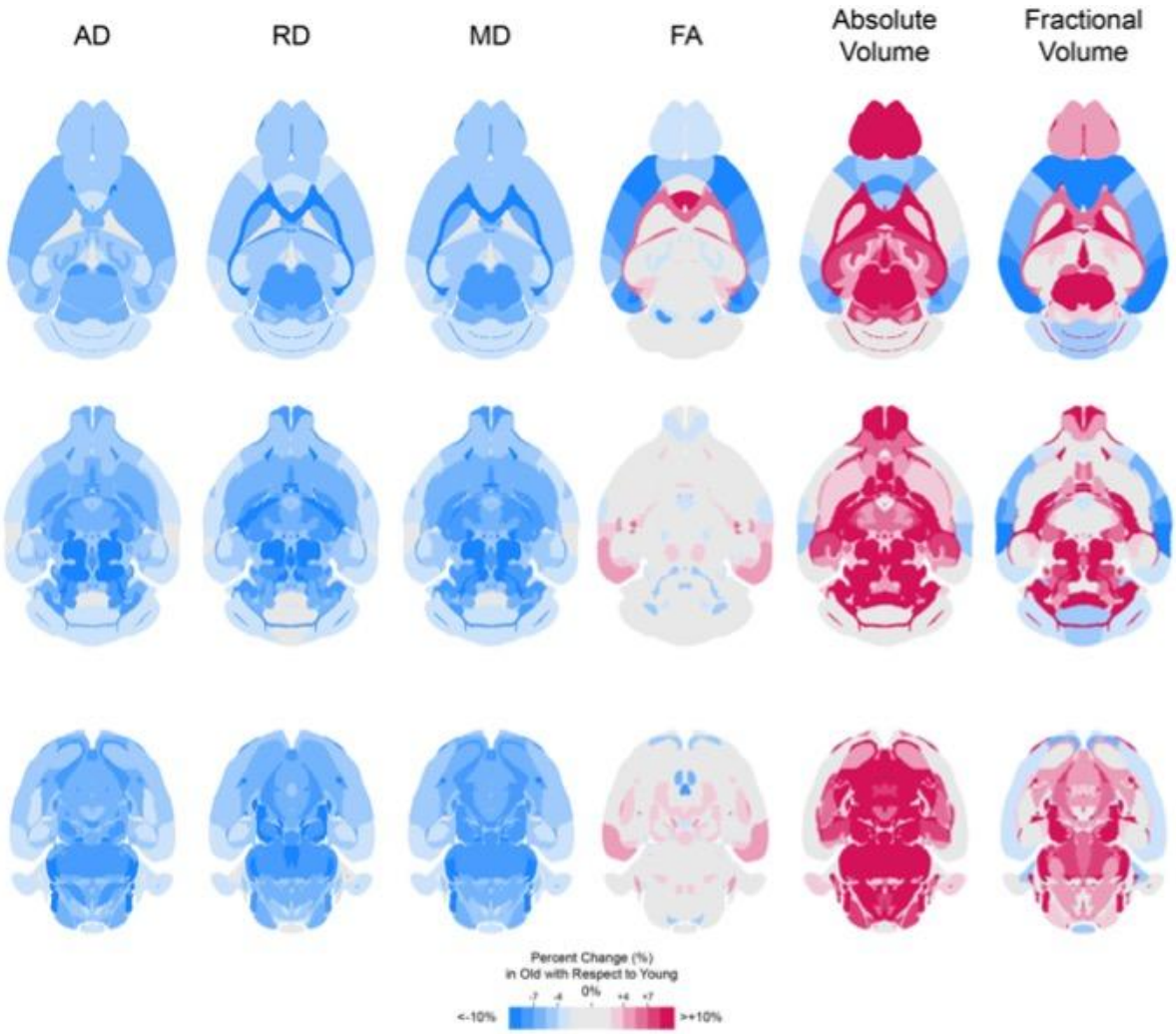
Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA Grant R01AG070913
NC Biotechnology Center Grant 2021-IIG-2101
NIH/NINDS Grant R01NS120954

Title: Statistical atlases of the aging mouse neurophenome

Authors: *L. E. WHITE[1], K. J. HORNBURG[2], J. COOK[2], W. AUSTIN[2], Y. QI[1], D. G. ASHBROOK[3], R. W. WILLIAMS[4], G. A. JOHNSON[2];
[2]Radiology, [1]Duke Univ., Durham, NC; [3]Inst. for Neurosci. and Cardiovasc. Res., The Univ. of Edinburgh, Edinburgh, United Kingdom; [4]Genetics, Genomics, and Informatics, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: MRI is a powerful means for interrogating age-dependent change in the brain. The structural neurophenome derived from MRI provides a quantitative profile of age-related change based on: (1) morphology; (2) cytoarchitecture, using scalar diffusion MRI (dMRI); and (3) connectivity, defined by the structural connectome. We explored how these image derived phenotypes change in genetically divergent mouse models of aging using magnetic resonance histology (MRH) in perfusion fixed brains imaged in situ. MRH was performed on 127 mice. Statistical analysis included 107 animals in two age groups (young: 100 ± 10 days, n = 47; old: 477 ± 86 days, n = 60) from 13 different BXD strains. Diffusion tensor images were acquired at 45 μm, with 46 angles and b = 4000 s/mm^2 using the 9.4T Duke mouse connectome scanner. Data were registered to the Duke Mouse Brain Atlas delineating a subset of 231 regions from the ABA common coordinate framework. Whole-brain, population atlases were created for young and old cohorts across and within strains. Differences between young and old are represented as statistical atlases, which encode various statistics of the diffusion scalar metrics and volumes in anatomical space. The figure shows percentage change in old versus young for scalar dMRI metrics and structure volumes at three axial planes. Diffusion metrics decreased in older animals, although fractional anisotropy (FA) increased in white matter due to greater decrease in radial diffusivity (RD) than axial diffusivity (AD). Striking changes in volumes were widespread with most neocortical areas decreasing and most subcortical structures increasing. Strain-stratified analyses indicate that genetic background modulates age-dependent change, with some strains showing greater resilience or vulnerability. These results provide the foundation for future studies of the structural neurophenome and how biological factors, such as genetic background and sex, as well as modifiable factors such as diet and activity, may alter the trajectory of aging throughout the brain.



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Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.12/T28

Topic: C.01. Brain Wellness and Aging

Title: Assessing Adult Hippocampal Neurogenesis Across Sex and Age in the Common Marmoset

Authors: *S. E. ENRIGHT[1], S. L. PARYLAK[2], F. H. GAGE[3], J. C. MARTINEZ-TRUJILLO[4]; [1]Univ. of Western Ontario, London, ON, Canada; [2]LOG-G, Salk Inst., La Jolla, CA; [3]LOG-G,

Salk Inst. for Biol. Studies, La Jolla, CA; [4]Dept. of Physiol. and Pharmacol. and Psychiatry, Western Univ., London, ON, Canada

Abstract: Adult hippocampal neurogenesis (AHN) has been extensively reported in rodents, with several studies documenting the developmental and maturation processes of adult-born cells. In mammals, AHN occurs in the dentate gyrus (DG) and has been implicated in learning, memory, and other hippocampal-specific processes. However, studies have reported that AHN seems to present at lower levels in humans, and neurogenic rates are widely disputed. Additional research analyzing AHN in non-human primate (NHP) models is necessary to further understand species-specific differences to effectively translate this knowledge to humans. Here, we use dual labelling with bromodeoxyuridine (BrdU) and ethynyl deoxyuridine (EdU) to quantify AHN and explore survival rates of adult-born neurons in a small primate, the common marmoset (Callithrix jacchus). Our results show several adult-born neurons within the subgranular zone (SGZ) of the DG with declining rates associated with age. Neurogenic rates differ between mice and marmosets, suggesting differences in AHN are likely related to the species' lifespan and may be an evolutionary adaptation to optimize stability in neuroplasticity. We also explore novel methods to examine morphological distinctions between adult-born neurons of non-human primates (NHPs) and rodents, as well as the resulting impacts on circuits and behaviour. We propose that the common marmoset may serve as an essential intermediate model to translate data from rodent models to human studies, providing insight into neuropsychiatric and neurodegenerative disorders that affect AHN and memory.

Disclosures: S.E. Enright: None. **S.L. Parylak:** None. **F.H. Gage:** None. **J.C. Martinez-Trujillo:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.13/T29

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG050782
NIH Grant R01AG056519
NIH Grant R01AG052142
NIH Grant R01AG031563

Title: Associations between early/midlife emotional distress, anxiety, and depressive symptoms and brain volume in older adulthood

Authors: *M. R. LAPOINT[1], J. N. ROSCOE[1], S. T. FARIAS[2], R. WHITMER[3], P. GILSANZ[1]; [1]Kaiser Permanente Northern California Div. of Res., Pleasanton, CA; [2]Dept. of Neurol., [3]Dept. of Publ. Hlth. Sci. and Neurol., Univ. of California, Davis, Sacramento, CA

Abstract: Late-life mental health is associated with brain atrophy, but relationships between early/midlife emotional distress and later brain health are unclear. 596 participants from 3 cohort studies completed 1+ early/midlife health survey (mean age at survey=35) including emotional distress, anxious symptoms, or depressive symptoms items and received an MRI (mean age at MRI=75).
We created 4 binary distress variables: any distress (endorsement of 1+ general, anxious, or depressive symptom); general distress (1+ general); anxiety (1+ anxious), depression (1+ depressive). Brain volumes included intracranial-volume adjusted cortical gray matter, hippocampal, ventricular, and lobar volumes (frontal, occipital, parietal, temporal). Linear regression modeled estimated associations between early/midlife distress and brain outcomes adjusting for MRI age, time between MRI and survey, demographics, and cohort.
142 participants experienced any distress, 84/544 experienced general distress, 74/271 experienced anxious symptoms, and 81/266 experienced depressive symptoms.
Depressive symptoms were associated with smaller temporal volume (β=-2.02 [95% CI -3.93, -0.10]). Depressive symptoms were not associated with other brain imaging outcomes. This is in line with other work showing smaller temporal volume in older adults with later-life depressive symptoms and could be associated in part with previously observed depression-related disruption of limbic networks and temporal connectivity.

***Table 1**: Participant demographics & descriptive statistics*

Variable	***Participants (N=596)***
Sex/gender (N (%))	
Male	256 (43.0%)
Female	340 (57.0%)
Race and ethnicity (N (%))	
Asian	103 (17.3%)
Black	232 (38.9%)
Latinx	68 (11.4%)
White	132 (22.1%)
Multiracial	51 (8.6%)
Other/NA/refused	10 (1.7%)
Scan age, years	
Mean ± standard deviation	78.7 ± 8.7
Range	59.6-103.4
MHC age, years	
Mean ± standard deviation	34.0 ± 6.5
Range	25.0-58.0
Scan-MHC interval, years	
Mean ± standard deviation	44.7 ± 6.6
range	33.3-58.1
Study* (N (%))	
KHANDLE	365 (61.2%)
STAR	157 (26.3%)
LA90	74 (12.5%)
Education (N (%))	
≤ High school	85 (14.3%)
Some college/trade school	218 (36.6%)
≥College	293 (49.1%)

**Studies: KHANDLE: Kaiser Healthy Aging and Different Life Experiences study; STAR: Study of Healthy Aging in African Americans; LA90: LifeAfter90*

Table 2: *Associations between early/midlife emotional distress and brain volumes. Point estimates and 95% confidence intervals are reported.*

	Gray matter β [95% CI]	Hippocampal β [95% CI]	Frontal β [95% CI]	Parietal β [95% CI]	Occipital β [95% CI]	Temporal β [95% CI]	Ventricular β [95% CI]
Any symptoms (N=596) *No: 454; Yes: 142*	2.92 [-4.85, 3.32]	-0.01 [-0.15, 0.12]	-0.12 [-2.14, 1.90]	-0.30 [-1.80, 1.21]	-0.33 [-1.55, 0.89]	-0.28 [-1.73, 1.17]	-1.48 [-5.16, 2.20]
General symptoms (N=544) *No: 460; Yes: 84*	1.96 [-2.19, 6.11]	0.08 [-0.21, 0.04]	0.52 [-1.65, 2.69]	0.74 [-0.80, 2.28]	-0.15 [-1.38, 1.09]	0.95 [-0.58, 2.48]	-0.05 [-3.25, 3.15]
Anxious symptoms (N=271) *No: 197; Yes: 74*	0.41 [-4.96, 5.78]	-0.08 [-0.25, 0.10]	-1.06 [-3.74, 1.61]	-0.34 [-2.35, 1.68]	-0.31 [-1.84, 1.22]	0.14 [-1.69, 1.97]	-0.32 [-4.69, 4.05]
Depressive symptoms (N=266) *No: 185; Yes: 81*	-1.04 [-5.92, 3.85]	-0.08 [-0.24, 0.09]	-0.53 [-3.05, 1.99]	-0.33 [-2.35, 1.69]	0.62 [-0.87, 2.12]	-2.02 [-3.93, -0.10]	-1.18 [-5.77, 3.42]

Disclosures: M.R. LaPoint: None. **J.N. Roscoe:** None. **S.T. Farias:** None. **R. Whitmer:** None. **P. Gilsanz:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.14/T30

Topic: C.01. Brain Wellness and Aging

Support: Wellcome Trust 209453/Z/17/Z

Title: The Role of Cell Fusion in Maintaining and Restoring Cerebellar Function

Authors: *B. THEWLIS, E. M. M. MEYER, S. BAKER, P. T. CHADDERTON, K. C. KEMP; Univ. of Bristol, Bristol, United Kingdom

Abstract: Developing effective strategies to replace or restore injured neurons could transform the treatment of currently incurable neurodegenerative disorders. Previous studies have demonstrated that bone marrow-derived cells (BMDCs) can migrate into the brain and fuse with damaged Purkinje neurons (PNs), restoring aspects of their structure and function. However, despite more than two decades of research, the temporal dynamics and long-term functional stability of these fusion events *in vivo* remain poorly understood. Using longitudinal *in vivo* two-photon imaging of the intact cerebellum in EGFP bone marrow chimeric mice, we directly visualised BMDC-PN fusion events and tracked the physiological characteristics of fused neurons. Here, we provide definitive evidence that fused Purkinje neurons are not transient but remain stable within the living brain for prolonged periods. Furthermore, we demonstrate sustained transcriptional activity of donor-derived genes within fused neurons, indicating persistent integration of the BMDC nucleus. In parallel, whole-brain light-sheet fluorescence microscopy was used to generate high-resolution, three-dimensional mapping of BMDC

infiltration and fusion events across the entire cerebellum, enabling accurate quantification of rare fusion events at the whole-tissue scale. Together, these findings establish the long-term stability of BMDC-PN fusion events and provide new insight into the mechanisms underlying cell fusion-mediated neuronal repair. This work has important implications for the development of cell-based therapies, targeted gene delivery strategies, and regenerative approaches for cerebellar disease.

Disclosures: B. Thewlis: None. **E.M.M. Meyer:** None. **S. Baker:** None. **P.T. Chadderton:** None. **K.C. Kemp:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.15/T31

Topic: C.01. Brain Wellness and Aging

Support: R01 AG 079957
RF1 AG 082201

Title: Local Brain Age Gap Across Hippocampal Subfields: Phenotypic Architecture and a Subfield-Resolved Genome-Wide Analysis in the UK Biobank

Authors: *A. MISHRA, N. KIM, N. CHOWDHURY;
USC, Los Angeles, CA

Abstract: The brain age gap (BAG), the difference between predicted and chronological brain age, is a candidate biomarker of neurodegeneration. Prior genetic studies examined global and regional BAG, but the hippocampus has not been resolved at the subfield level. This resolution matters because hippocampal subfields differ in vulnerability to aging and Alzheimer's pathology, so a single hippocampal measure may obscure subfield-specific genetic signals. We present the first subfield-resolved analysis of the hippocampal local brain age gap (LAG) and its genetic architecture. We analyzed UK Biobank T1-weighted MRI from 41,859 cognitively normal participants (21,983 female; ages 45-83 yr). A deep learning model predicted voxel-level brain age, and LAG was computed as predicted minus chronological age. FreeSurfer segmentation yielded mean LAG in 12 bilateral subfields (24 total). Left and right subfields were analyzed separately to preserve hemispheric differences. Estimates from fewer than 10 voxels were masked for reliability. Across subjects, subfields were highly correlated, with the first principal component accounting for 99% of variance. Hippocampal brain aging is therefore governed largely by a single subject-level axis rather than independent per-subfield signals. This redundancy indicates that the twelve subfields largely reflect one heritable aging dimension, making genetic correlation across subfields the key test of whether finer anatomical resolution yields distinct biology. We also found a small, consistent right-greater-than-left LAG of approximately 0.26 yr, traced to the brain age maps themselves rather than to segmentation.

Genome-wide association testing of 655,421 SNPs against each subfield's LAG used linear regression adjusted for age, sex, five genetic principal components, and assessment center, in approximately 41,300 participants. Significance was set at Benjamini-Hochberg FDR-corrected p less than 0.05. We will report FDR-significant loci, nearest genes, and bivariate genetic correlations testing shared vs. distinct signals at the meeting. This work establishes the phenotypic and genetic structure of hippocampal aging at subfield resolution to determine whether subfield mapping adds information beyond a single hippocampal aging axis, with implications for future regional brain-age genetics.

Disclosures: A. Mishra: None. **N. Kim:** None. **N. Chowdhury:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.16/T32

Topic: C.01. Brain Wellness and Aging

Title: Age-Related Differences in Inhibitory Control and Decision-Making During CARIT Task fMRI

Authors: *D. ZIADLOU[1], T. CANLI[2];
[1]SUNY Stony Brook Integrative Neurosci. in Psychology, Selden, NY; [2]Dept Psychol, Stony Brook Univ., Stony Brook, NY

Abstract: Impulsivity is a multidimensional construct, which involves both reduced inhibitory behavioral control and a tendency to favor immediate over delayed rewards. In aged individuals, performance-based tasks can reveal vulnerability in inhibitory control when demands on control are high. For example, in Go/NoGo tasks, repeated Go trials strengthen the tendency to respond, making subsequent NoGo trials a stronger test of stopping. We used the conditioned approach response inhibition task (CARIT) behavior and task-fMRI from the Aging Adult Brain Connectome (AABC)/Human Connectome Project Aging (HCA) Release 2, to test whether response-history context reveals age-sensitive vulnerability in inhibitory control and whether these effects are related to delay discounting and recruitment of attention/control networks. Analyses included 1,368 behavior sessions and 1,211 imaging sessions. False-alarm rates differed across response-history conditions, indicating that inhibitory performance depended on the recent task context rather than being uniform across NoGo trials: 12.6% after two Go trials, 14.2% after three Go trials, and 10.4% after four Go trials. When we modeled false-alarm errors across NoGo trials (n=1,018), older age predicted higher false-alarm odds (odds ratio [OR]=1.18 per SD, z=7.99, p=1.4e-15) while controlling for delay-discounting area under the curve (AUC), control-network activity, sex, and Big Five personality traits. AUC was not associated with false alarms (OR=0.98, p=0.285), but higher AUC predicted lower Go-omission odds (OR=0.82, p=3.0e-19), indicating that age was more strongly related to failed stopping, whereas delay discounting was more closely related to missed Go responses. Task-fMRI examined neural

sensitivity to response history using a priori contrast of correct NoGo trials after four versus two preceding Go trials. Higher AUC was associated with stronger prepotency-sensitive activation in a dorsal attention/parietal region (t=3.90, false discovery rate [FDR] q=0.00057), dorsal attention network (t=2.96, q=0.013), and cingulo-opercular/dorsal attention network (t=2.98, q=0.013). Older age was associated with sensitivity to default-network prepotency (t=3.53, q=0.0053). The results showed that aging was associated with greater vulnerability to false-alarm errors. In contrast, delay discounting was linked to Go omissions and stronger recruitment of attention/control networks during successful inhibition, but not to false alarms. Together, these findings suggest that response-history context indicates how aging affects inhibitory control.

Disclosures: D. Ziadlou: None. **T. Canli:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.17/U1

Topic: C.01. Brain Wellness and Aging

Support: P01-AG055365
R01-DC019394
SMA1734892
T32-DC00046

Title: Age-related changes in white-matter structural connectivity are associated with auditory functional network organization and behavioral performance

Authors: *B. GUO[1], V. COMMURI[2], J. Z. SIMON[3];
[1]Univ. of Maryland, Col. Park, Potomac, MD; [2]Univ. of Maryland Col. Park, Wheaton, MD;
[3]Electrical and Computer Engin., Univ. Maryland, Col. Park, College Park, MD

Abstract: Cortical auditory processing relies on distributed communication among specialized cortical areas. Signals are transmitted between cortical areas through structural connections formed by white matter pathways in the brain. Nonuniform cortical atrophy is a widely reported phenomenon associated with aging, and is known to affect structural connectivity by altering lengths of structural connections between cortical regions. An important question is how these changes in structural connectivity relate to changes in functional connectivity. We apply deterministic tractography to diffusion tensor imaging (DTI) data to reconstruct white matter tracts connecting areas within parcellated cortex, and compute connection lengths from the resulting tractography. We then employ a whole-connectome mixed-effects regression analysis that relates structural connectivity between cortical regions to functional and behavioral measures. We utilize a combination of cluster testing and counterfactual modeling to establish significance of specific effects within the model hierarchy. The results show significant association between structural decline and functional changes that accompany aging. These

effects were localized to subnetworks implicated in auditory and higher-order cognitive processing. Structural connectivity measures were further associated with behavioral measures relevant to speech listening. Taken together, these results suggest that age-related changes in white matter architecture affect speech-listening performance through their influence on inter-regional functional communication. We demonstrate how to combine structural and functional networks to analyze specific behavioral factors that form one part of a hierarchy of effects that contribute to age-related difficulty in speech listening. The results stand to improve our understanding of how aging affects speech-listening circuits in the brain. Behavioral factors identified could lead to improvements in targeted training, which could inform socio-environmental outcomes for older adults.

Disclosures: B. Guo: None. **V. Commuri:** None. **J.Z. Simon:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.18/U2

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01AG047972
NIH Grant R01AG029523
NIH Grant R01NS106711
NIH Grant R01NS106702

Title: Availability of Processing Speed-Related Neural and Vascular Resources Distinguishes Faster from Slower Working Memory Performance in Older Adults

Authors: *E. SMITH MCGUIRE[1], Y. ZHAO[2], M. ANDREO[1], G. SHERARD[1], D. H. ABDELKARIM[1], V. PRABHAKARAN[3], B. P. RYPMA[1];
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Neurobio. and Behavior, Univ. of California, Irvine, Irvine, CA; [3]Dept Neurosci, Univ. of Wisconsin, Madison, WI

Abstract: Age-related differences in processing speed have been identified as a primary factor mediating age-related differences in working memory (WM) performance. However, the extent to which processing speed-related neural activity accounts for WM-related performance is not yet known. We hypothesized that recruitment of dorsolateral prefrontal cortex (dlPFC; involved in processing speed and WM) during an in-scanner parametric digit-symbol task would differ in older adults (OA) with faster vs. slower WM performance. 41 healthy OAs (M_{age} = 61.85, SD_{age} = 4.75) performed a Sternberg WM (SWM) task, in which they were shown 6 letters for 2000 ms. Either 2, 4, or 6 of these letters were bracketed, indicating the letters to be remembered. Following a 4000 ms maintenance interval, a single probe letter appeared, and participants indicated whether that letter was among those initially appearing in brackets. During scanning, participants also completed the Digit-Symbol Verification Task (DSVT), a scanner-adapted

digit-symbol task used to assess processing speed. A key of either 1, 3, or 9 digit-symbol pairs appeared above a fixation cross, and a single digit-symbol probe appeared below the fixation cross. Participants were instructed to indicate whether the digit-symbol probe matched one of the pairs in the key. Participants' SWM reaction time slopes were computed. Participants were separated into either low-slope (faster) or high-slope (slower) groups, via median split, to distinguish faster from slower WM performers. We assessed differences in DSVT blood-oxygen-level-dependent (BOLD) and cerebral blood flow (CBF) percent signal change (PSC) in dlPFC between faster and slower WM groups. We observed that faster WM performers showed a significant stepwise increase in dlPFC BOLD PSC from DSVT set size 3 to set size 9 (paired t = 3.55, p = .002), and significantly higher CBF PSC from the lowest to the highest DSVT set size (paired t = 2.32, p = .03). While slower WM performers showed a significant increase in DSVT BOLD PSC from DSVT set size 3 to set size 9 (paired t = 2.48, p = .02), no differences were found in DSVT CBF PSC from the lowest to the highest DSVT set size (paired t = 0.79, p = .44). Faster WM performers also showed significantly higher DSVT BOLD PSC than slower WM performers only at the highest task load (t = 2.21, p = .03). These results indicate that increased availability of processing speed-related neural resources, possibly due to relatively preserved vascular function, affords faster WM performance among OAs. In follow-up analyses, we will continue to investigate the physiological mechanisms (i.e., CBF, cerebral metabolic rate of oxygen) that underly these phenomena.

Disclosures: E. Smith McGuire: None. **Y. Zhao:** None. **M. Andreo:** None. **G. Sherard:** None. **D.H. Abdelkarim:** None. **V. Prabhakaran:** None. **B.P. Rypma:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.19/U3

Topic: C.01. Brain Wellness and Aging

Title: The Influence of Aging onPerineuronal Nets in thePigeon Telencephalon

Authors: *H. RUBY[1], E. SHULTZ[2], L. KINNEY[3], J. WILLING[2], V. P. BINGMAN[2]; [2]Psychology, [1]Bowling Green State Univ., Bowling Green, OH; [3]Bowling Green State Univ., Perrysburg, OH

Abstract: Perineuronal nets (PNNs) are mesh-like structures within the extracellular matrix that surround particular neurons and play a critical role in cell protection, regulation of neuronal excitability, and the modulation of synaptic plasticity. Due to these broad neuronal support functions, PNNs have been widely studied, including research on neurodegeneration. However, variability in the distribution and structure of PNNs across species and brain regions has also made them of interest to comparative neurobiologists. In the present study, we investigated the presence of PNNs in the telencephalon of juvenile and elderly pigeons- a novel animal model in the field of PNN and aging research. To compare PNN distribution and abundance between

young and aged subjects, we conducted PNN counts within two regions that seem to be particularly affected by aging- the nidopallium caudolaterale (NCL) and the hippocampus. The avian hippocampus is of particular interest given the advanced spatial navigational abilities of pigeons and previous findings that suggest pigeons, despite age-related deficits in spatial memory, exhibit increases in hippocampal volume with age. Our work is the first to identify PNNs within the pigeon telencephalon and may offer a partial explanation for the paradox of age-associated deficits in spatial cognition despite observed increases in hippocampal volume.

Disclosures: H. Ruby: None. **E. Shultz:** None. **L. Kinney:** None. **J. Willing:** None. **V.P. Bingman:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.20/U4

Topic: C.01. Brain Wellness and Aging

Support: NMSS RG-1507-04951

Title: Go With the Glymphatic Flow: Relationships Between Glymphatic Pathways and Cognition in Healthy Aging

Authors: *M. ANDREO[1], D. SIVAKOLUNDU[2], M. D. ZUPPICHINI[3], K. WEST[1], B. P. RYPMA[4];
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Dept. of Biol. Sci., Univ. of Texas at Dallas, Dallas, TX; [3]Psychology Dept., Univ. of Michigan, Montclair, NJ; [4]Behavioral & Brain Sci., Univ. of Texas At Dallas, Dallas, TX

Abstract: The glymphatic system is thought to facilitate clearance of metabolic waste from the brain. In this system, metabolic waste clearance is initiated by influx of cerebrospinal fluid (CSF) via choroid plexus (CP). The CSF enters the periarterial perivascular spaces, interacts with interstitial fluid (ISF), and picks up metabolic waste before exiting into perivenous spaces via meningeal lymphatic vessels (mLVs) and other pathways. Impaired glymphatic function has been mainly investigated as a physiological mechanism for cognitive changes associated with age-related neurodegenerative diseases. Less work has been done to elucidate relationships between glymphatic-system function and cognitive abilities (e.g., processing speed) in healthy aging. 36 healthy adults (M_{age}=42.97, SD=12.43) were scanned using magnetic resonance imaging (MRI) and performed cognitive testing. MRI scanning included a magnetization-prepared rapid gradient-echo (MPRAGE) scan to quantify CP volumes, a fluid-attenuated inversion recovery (FLAIR) scan to quantify mLV volumes, and a diffusion tensor imaging (DTI) scan to calculate water diffusivity along perivascular spaces (DTI-ALPS). DTI-ALPS has been proposed as a non-invasive global measure of glymphatic function in humans. Cognitive testing included the following: Digit Symbol Substitution Test (DSST), Symbol Digit Modalities

Test (SDMT), Box Completion Test (BCT), Trail Making Test (TMT), Number Comparison Test (NCT), 10/36 (number correct and commission errors in immediate and delayed recall), and Paced Auditory Serial Addition Test (PASAT; 2 and 3 second intervals). Age was correlated with CP volume ($r = 0.45$, $p < .01$) and DTI-ALPS ($r = -0.63$, $p < .01$), but not with mLV volume ($r = -0.02$, $p = .88$). By using multiple linear regressions that covaried for total brain volume and age, increases in CP volume were related to slower performance on a processing-speed composite comprised of DSST, SDMT, and BCT ($\beta = -0.38$, $p = .022$). Increases in mLVs predicted increases in commission errors that occurred during immediate ($\beta = 0.34$, $p = .023$) and delayed recall ($\beta = 0.33$, $p = .041$) on the 10/36 test. DTI-ALPS did not significantly predict cognitive performance on the tasks. Thus, whereas larger CP volumes were associated with poorer performance in processing-speed tasks, increases in mLV volumes were associated with poorer performance in immediate and delayed visuospatial memory. Age-related differences in glymphatic-system indices, specifically the influx and efflux pathways (CP and mLVs), may play a role in the physiology underlying cognitive decline seen in healthy aging.

Disclosures: M. Andreo: None. **D. Sivakolundu:** None. **M.D. Zuppichini:** None. **K. West:** None. **B.P. Rypma:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.21/U5

Topic: C.01. Brain Wellness and Aging

Support: 1R01AG079799

Title: Aging-related Transcriptomic Changes with Spatial and Cell Type-Specific Resolution in the Human Prefrontal Cortex

Authors: *A. RAI[1], A. IATROU[2,3,5], I. VALENZUELA ARZETA[6], A. BARTLETT[9], J. BANAHAN[6], V. DESAI[10,6], N. SOHAIL[9], I. CASTANHO[6], P. NADERI YEGANEH[6], A. PLOUMAKIS[6,11,13,14], S. WANG[7,13,16,11], A. ARRUDA DE AMARAL[6,14,13,11], P. TSVETKOV[6], S. BERRETTA[4], I. SOLOMON[17], W. HIDE[8,18], I. VLACHOS[6,14,13,11], F. SLACK[6,14], R. A. OZDEMIR[19], S. HO SUI[9], N. DASKALAKIS[20,3,21,22,12], M. MAVRIKAKI[6,15];
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Israel Deaconess Med. Ctr., Boston, MA; [15]Harvard Med. Sch. Initiative for RNA Med., [14]Harvard Med. Sch. Initiative for RNA Medicine, Harvard Med. Sch., Boston, MA; [16]Harvard Med. Sch. Initiative for RNA Medicine, Harvard Med. School, Boston, Boston, MA; [17]Dept. of Pathology, Brigham and Women's Hospital, Harvard Med. School, Boston, MA, 02115, USA, Boston, MA; [18]Harvard Med. Sch., Harvard Med. Sch. Initiative for RNA Med., Boston, MA; [19]Berenson Allen Ctr. for Nononvasive Brain Stimulation, Dept. of Cognitive, Dept. of Neurology, Beth Israel Deaconess Med. Center, Harvard Med. Sch., Boston, MA; [20]Psychiatry, Harvard Med. School/Mclean Hosp., Boston, MA; [21]Dept. of Pharmacology, Physiol. and Biophysics, [22]Dept. of Med. (Biomedical Genetics), Boston Univ. Chobanian & Avedisian Sch. of Med., Boston, MA

Abstract: The human prefrontal cortex (PFC), whose laminar organization is essential for cognitive function, is among the first regions to show age-related functional decline. Single-cell sequencing studies revealed cell type-dependent aging effects, but lacked spatial specificity. Here, we performed spatial transcriptomics (ST) on postmortem PFC from 37 individuals across the adult lifespan (18-97-years-old). We compared transcriptomic profiles in early adulthood (18-40-years old) to profiles in late adulthood (>70-years old) to characterize age-related molecular changes within each cortical layer and white matter (WM), and across cell types within those spatial domains. Our findings reveal both shared mechanisms of aging across cortical layers and cell types, as well as layer- and cell type-specific pathways that contribute to heterogeneity of aging processes. Interestingly, we also found that the proportion of inhibitory GABAergic interneurons, specifically those expressing RELN, SST, and PVALB, decreased while the proportion of astrocyte subtypes (Astro-FB & Astro-PP)- increased with aging. Alterations in cell-cell interactions in aging among spatially resolved subtypes of excitatory neurons, inhibitory neurons, astrocytes, microglia, and endothelial cells was revealed by changes in interaction strengths and qualitative shifts in ligand-receptor signaling pathways, highlighting a reorganization of the cortical cell-cell communication landscape. This represents comprehensive lifespan ST analysis of the human PFC , offering new insight into cortical aging and potential to identify targets to modulate cognitive aging.

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Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.22/U6

Topic: C.01. Brain Wellness and Aging

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VA-RR&D (B.C.: D2354R)
NIH-NIA (W.M.H. and P.R.M.: R56 AG080735)
NIH-NIDA (K.T.K.: R01-DA048096)

Title: Emotional word processing elicits age- and valence-specific patterns of neurotransmitter release in the ventral intermediate nucleus of the human thalamus

Authors: *J. L. BARBARO[1,3], S. R. BATTEN[3], H. NGUYEN[3], P. SANDS, III[3], A. HARTLE[3], L. BARBOSA[3], B. HADJ-AMAR[7], D. BANG[8,3,9,10], N. MELVILLE[3], T. TWOMEY[3], J. P. WHITE[3], T. M. LOHRENZ[3], K. T. KISHIDA[11,12], M. R. WITCHER[2,3], M. VANNUCCI[7], S. M. MCCLURE[13], B. CASAS[3,4], P. H. CHIU[3,4], W. M. HOWE[5], P. MONTAGUE[3,9,6];
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Abstract: Aging is associated with a suite of cognitive and behavioral changes, including the processing of emotionally valenced stimuli. In particular, previous work has described a "positivity bias" or prioritization of positive over negative information processing associated with aging. The neural mechanisms that underlie these age-related changes in affective processing are not clear, though stimulus-evoked fluctuations of the release of monoamine neurotransmitters (dopamine; DA, norepinephrine; NE, serotonin; 5HT) are hypothesized to be essential for encoding stimulus valence and are also subject to age-related changes. To better characterize the potential relationship between age, monoamine release, and valence processing, here we utilized a machine-learning enhanced approach to electrochemistry to characterize sub-second changes in DA, NE, and 5HT release in the ventral intermediary thalamus of conscious

humans (n=9, 60-83 years old) undergoing neurosurgery for the treatment of essential tremor. Stimulus valence encoding by monoamines was assessed with a word-valence task wherein subjects were presented with equal numbers of positively, negatively, and neutrally-valenced words selected from the Affective Norms for Emotional Words database. Task engagement was evaluated by prompting subjects to report the color of the word presented on screen. At the level of behavior, we noted that increasing age was associated with a trending increase in the time to report word-color, as well as an overall decline in word-color accuracy. Preliminary analyses of word-evoked DA, NE, and 5HT release revealed selective age and valence-related changes in NE release. Specifically, whereas DA and 5HT responses to valenced words were consistent across age, NE responses to positively-valenced words significantly declined with age. Our data suggest that the aging brain undergoes distinct neurochemical changes during emotional valence processing, and that dysregulation of NE release may be related to the positivity bias. Ongoing studies seek to understand the larger cognitive and behavioral domains associated with age-related changes in sub-second monoamine release dynamics and how they might relate to future disease states.

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Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.23/U7

Topic: C.01. Brain Wellness and Aging

Title: Changes in Brain Vasculature in Carollia perspicillata: Young vs. Old

Authors: *K. P. VON MAYDELL, R. KOLLMAR, M. STEWART, R. ORMAN;
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Abstract: Cerebrovascular dysfunction is increasingly recognized as a major contributor to brain aging and neurodegenerative disease. Age-related changes in cerebral blood vessels can result in reduced perfusion, impaired neurovascular coupling, chronic neuroinflammation, decreased clearance of toxic metabolites, and disruption of the blood-brain barrier. These factors have been shown to play a role in the development of cognitive decline and dementia in humans. Recent evidence suggests vascular pathology may precede or even drive neuronal dysfunction in aging-related neurodegenerative diseases like Alzheimer's disease as opposed to occurring as a consequence of neurodegeneration. Contractile mural cells, which include vascular smooth muscle cells and subsets of pericytes, are critical regulators of both cerebral blood flow and vascular stability. These cells express alpha smooth muscle actin (α-SMA/ACTA2), which is a

cytoskeletal protein that contributes to vascular contractility and regulation of cerebral blood flow. Therefore, prior work has characterized changes in α-SMA expression using immunoblotting and immunohistochemistry using rodents as the primary model. Although rodents remain the dominant model for studying brain aging, they possess key limitations, including short lifespans, limited natural development of neurodegenerative pathology, and neuroanatomical differences from primate brains. Many rodent aging studies therefore rely on accelerated or transgenic disease models that may not fully recapitulate naturally occurring age-related neurovascular decline.
In contrast, our lab model, Seba's short tailed fruit bat a.k.a. Carollia perspicillata, lives an average of 12.4 years in captivity and shares many similarities with human brain anatomy including in regions first impacted by pathologic brain aging like the hippocampus. Thus, bats offer a useful platform for studying vascular changes with age that reflects the gradual cerebrovascular and neuropathological changes observed in humans. In this study, immunohistochemical analysis of α-SMA was performed in bat brain tissue collected from young and aged animals to evaluate age-related differences in vascular morphology and mural cell-associated staining patterns. Brain sections were processed using standardized immunohistochemical methods, microscopy and image analyses for regional and age-dependent differences in α-SMA immunoreactivity.

Disclosures: K.P. von Maydell: None. **R. Kollmar:** None. **M. Stewart:** None. **R. Orman:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.24/U8

Topic: C.01. Brain Wellness and Aging

Title: Region and Sex-Specific Inflammatory and Intracellular Signaling Alterations During Normative Aging

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Abstract: Aging is the primary risk factor for cognitive decline, yet the molecular mechanisms underlying brain aging remain incompletely understood. Emerging evidence suggests that aging does not uniformly increase inflammatory signaling across the brain; instead, neuroimmune alterations may be region-, sex-, and cell-type-specific. In rodents, cortical aging is associated with synaptic loss, glial activation, vascular dysfunction, and the expression of senescence-related genes, with distinct molecular signatures reported in neurons, astrocytes, oligodendrocytes, and microglia. To investigate age-related neuroimmune signaling, young adult (PND100) and aged (2+ year) male and female Sprague-Dawley rats were examined. Dorsal and

medial superficial cortical tissue was collected by gently scraping the upper cortical surface while excluding visible myelin-rich tissue to enrich for superficial cortical gray matter. Additional analyses were conducted in hippocampal commissure and pineal gland tissue. Protein expression of inflammatory and signaling markers, including NFκB, phospho-NFκB, Iba1, ERK, and phospho-ERK, was assessed by Western blot. Preliminary findings indicate that aging produces region- and sex-specific alterations in neuroimmune signaling. In cortical sheath tissue, phospho-ERK expression increased with age in both males and females. In contrast, total NFκB expression exhibited a significant Sex × Age interaction. Post hoc analyses revealed that aged females displayed significantly lower NFκB expression than aged males, whereas males exhibited little age-related change. These findings suggest that sex differences in cortical NFκB signaling emerge during aging rather than being uniformly present across the lifespan. Ongoing analyses are evaluating age-related alterations in microglial-associated signaling, vascular-associated immune pathways, and white matter-related neuroimmune markers across cortical, commissural, and neuroendocrine brain regions. Together, these findings support the hypothesis that normative aging produces distinct neuroimmune signatures across brain interfaces and that aging-related changes in inflammatory signaling are influenced by both sex and regional cellular composition.

Disclosures: S. Azerrad: None. **P. Sack:** None. **M. Enos:** None. **A.J. Betz:** None.

Poster

PSTR048: Neural Mechanisms of Aging

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR048.25/U9

Topic: C.01. Brain Wellness and Aging

Support: Oregon Health Sciences University Center For Women's Health Circle of Giving

Title: Brain Dynamics across the Menopause Transition

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Abstract: Background: The menopausal transition is marked by fluctuations in hormone levels, like estrogen, which lead to a broad range of somatic and cognitive symptoms that impact the general well-being of aging women. It may be that changes occur on the level of brain networks as estrogen plays a role in the reorganization and connectivity of brain circuitry, thus impacting cognition. Hormone therapy (HT) is used to offset menopause related fluctuations, but the effectiveness of this treatment may be impacted by the time of onset. It is not yet understood how or which regions of connectivity are impacted by hormonal fluctuations or whether these changes are influenced by HT. Further, there are open questions with respect to the timing of the initiation of HT, as there may be a critical period for optimal initiation and impacts on brain

networks and cognition. **Methods:** Using resting state functional connectivity magnetic resonance imaging (fcMRI), we investigated changes in brain network organization and associations with hormonal fluctuations using a dense sampling approach. This study recruited 8 perimenopausal and postmenopausal women, (4 on and 4 off HT), to complete 24 weekly brain imaging scans, provide salivary hormonal samples, and complete questionnaires. **Results:** We expect to find fluctuations in cognitive brain networks across the menopause transition for each individual. These network fluctuations will likely be associated with hormonal fluctuations and menopause symptoms. Additionally, we expect to see an influence of the stage of menopause and HT on the extent and manner of these network changes. **Discussion:** Understanding how brain networks are impacted by hormonal fluctuations across the menopausal transition can provide insight into how cognition in aging women is treated. This is of particularly high clinical importance, given the higher incidence of Alzheimer's Disease in older females. This study will also provide further directions for the development and implementation of HT for menopausal women with respect to timing and impacts on brain dynamics. This richly sampled cohort allows for novel and needed insights into hormonal impacts on brain organization during a period of dynamic change in the female lifespan.

Disclosures: C.A. Delaney: None. **A.R. Weiss:** None. **J.A. Bernard:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.01/U10

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

Support: National Institute of Neurological Disorders and Stroke NS141137
National Institute of Aging AG075798
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Florida Education Fund (McKnight Doctoral Fellowship G.R.M.).

Title: Reducing Neutrophil Sialic Acid Residues Alleviates Cerebral Hypoperfusion in Alzheimer's Models

Authors: *J. JANULIS[1,2], N. BHATT[4,2], Z. TABRIZI[3,5], S. CHAKRABORTY[3,5], M. WEICK[5,6], S. FRANCIOSA[2], G. RODRIGUEZ[5,2], J. E. GALVIN[7], O. BRACKO[8,2];
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Abstract: Neutrophil activity has been shown to contribute to AD pathology, causing hypoperfusion by physically blocking capillary blood flow through adhesion and aggregation on vessel walls. However, little is known about the cell-surface modifications that promote this adhesion. Therefore, we investigated whether specific neutrophil surface glycosylation patterns are altered in AD.
Sialic acid (SA) residues are pro-translational terminal caps on surface glycoprotein chains that can regulate neutrophil adhesion to immune cells and vasculature. We used lectin blotting to show that SA residues are upregulated on neutrophil membranes in the 5xFAD mouse model. Furthermore, we evaluated the efficacy of the sialyltransferase inhibitor α2,3-sialyltransferase-IN-1 using lectin blot analyses, elucidating the compound's ability to remove SA from neutrophil membrane proteins.
Next, we performed in vivo multiphoton imaging to determine cerebral blood flow (CBF) and capillary stalling in 5xFAD and control mice following treatment with α2,3-sialyltransferase-IN-1. These findings demonstrated that sialyltransferase inhibitor-induced reductions in neutrophil SA residues improved CBF and decreased capillary stalling events in AD mice.
Lastly, we compared SA concentrations in human buffy-coat samples from control, preclinical AD, and mild cognitive impairment patients (MCI). Results from lectin blotting demonstrate significant upregulation of SA concentrations in MCI patients and milder upregulation in preAD patients compared with cognitively normal patients, indicating SA concentration is positively correlated with disease burden.
Our data provide evidence that SA is increased in neutrophils from AD models and patients, and could serve as a biomarker for vascular dysfunction in AD.

Disclosures: J. Janulis: None. **N. Bhatt:** None. **Z. Tabrizi:** None. **S. Chakraborty:** None. **M. Weick:** None. **S. Franciosa:** None. **G. Rodriguez:** None. **J.E. Galvin:** None. **O. Bracko:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.02/U11

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant NS122808
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Alzheimer's Association AARG-22-974437
Florida Department of Health (23A12)

Title: Recurrent hypoglycemia exposure impairs cognition via platelet-associated cerebral microvascular alterations in insulin-treated diabetic rats.

Authors: *A. K. REHNI[1], G. RODRIGUEZ[2], S. MALLEPALLI[1], P. POORVA[3], Z. TABRIZI[2], M. WEICK[2], O. BRACKO[2], K. R. DAVE[1];
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Abstract: Diabetes affects approximately 38 million people in the USA and chronic diabetes leads to cognitive dysfunction. Antidiabetic therapy causes transient hypoglycemia which increases the risk of recurrent hypoglycemia (RH). RH worsens cognitive outcome in diabetes[1]. We showed that RH exposure to insulin-treated diabetic (ITD) rats impairs spatial learning and memory, as assessed using the Barnes circular platform maze test[2]. Next, we tested the effect of chronic RH exposure on non-spatial declarative recognition memory, and spatial short-term working memory, in ITD rats. Diabetic rats received insulin pellet treatment 2-3 weeks after diabetes onset. The rats were randomly assigned to either hyperinsulinemic euglycemia (control) or hypoglycemia groups. RH exposure was started after 2-3 weeks. A subcutaneous insulin dose was used to induce non-severe hypoglycemia twice weekly for 3 hours for 4 weeks. The effect of RH exposure on cognition was assessed a week later using novel object recognition, and Y-maze spontaneous alternation tests to assess recognition memory, and spatial short-term working memory, respectively. RH-exposed ITD rats displayed a significantly decreased discrimination index (DI) (0.69±0.04, n=10; $p<0.05$) and percent alternation (58±3%, n=10; $p<0.05$) when compared to the DI (0.82±0.02, n=8) and percent alternation (69±3%, n=7) in controls, respectively, showing that RH exposure impairs recognition memory in rats. Microvascular alterations mediate cognitive impairment, and platelet activation modulates neurovascular function and CBF[3-4]. Therefore, we hypothesized that platelet-associated cerebral microvascular alterations mediate RH-exposure induced cognitive impairment in ITD rats. *In vivo* two-photon microscopy was utilized to examine cortical capillary blood flow, flux, and RBC volumetric flow rate. RBC flux was significantly lower, and capillary diameter was significantly higher in the RH-exposed ITD group when compared to the controls ($P < 0.05$ each). Moreover, RH-exposed rats exhibited a significant increase in stalled CD62p+ platelets ($P < 0.05$) compared with controls. Therefore, RH exposure decreases capillary perfusion and increases activated platelets associated with stalled capillaries in the cerebral vasculature in ITD rats. This study suggests that platelet dysfunction-induced decrease in cerebral blood flow may be responsible for observed cognitive impairment in RH-exposed ITD rats. References: 1) J. Neuroinflammation. 2012; 9: 182. 2) Transl. Stroke Res. 2019; 10(1): 78-90. 3) J. Physiol. 2025; 603(11): 3379-3404. 4) Brain Sci. 2021; 11(2): 140.

Disclosures: A.K. Rehni: A. Employment/Salary (full or part-time):; University of Miami Miller School of Medicine. **G. Rodriguez:** A. Employment/Salary (full or part-time):; University of Southern California. **S. Mallepalli:** A. Employment/Salary (full or part-time):; University of Miami Miller School of Medicine. **P. Poorva:** A. Employment/Salary (full or part-time):; University of Miami. **Z. Tabrizi:** A. Employment/Salary (full or part-time):; University of Southern California. **M. Weick:** A. Employment/Salary (full or part-time):; University of Southern California. **O. Bracko:** A. Employment/Salary (full or part-time):; University of South California. **K.R. Dave:** A. Employment/Salary (full or part-time):; University of Miami Miller School of Medicine.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.03/U12

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01NS121095
R01AG081841
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U19NS123717
U24EB028941

Title: Depth-resolved intravascular oxygen partial pressure imaging by 3-photon phosphorescence lifetime microscopy reveals reduced cerebrovascular reserve in deep cortex and white matter

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Abstract: Title: Depth-resolved intravascular oxygen partial pressure imaging by 3-photon phosphorescence lifetime microscopy reveals reduced cerebrovascular reserve in deep cortex and white matter
Abstract: White matter (WM) is among the earliest sites of pathological change in aging, neurodegeneration, and cerebrovascular disease, yet WM oxygenation remains poorly characterized due to the lack of tools capable of measuring oxygen partial pressure (pO_2) in vivo at depths beyond ~600 μm. Existing 2-photon imaging approaches are fundamentally limited by out-of-focus signal at greater imaging depths, leaving the deep cortical layers and WM microvascular network largely inaccessible. We developed 3-photon phosphorescence lifetime microscopy (3PLM) using an oxygen-sensitive phosphorescent nanoprobe (Oxyphor 2P), whose longer excitation wavelength and higher-order nonlinearity confine signal to the focal volume, enabling micrometer-resolution intravascular pO_2 measurements from the pial surface through the full cortical column and into subcortical WM in awake mice.
We applied 3PLM to compare intravascular pO_2 in young and aged mice under normal conditions, and in young mice under systemic hypoxia versus normoxia. In both young and aged mice under normal conditions, the range of intravascular pO_2 values narrowed significantly with depth in deep cortical layers and WM, indicating reduced cerebrovascular oxygen reserve in these regions. Aged mice additionally exhibited decreased arteriolar pO_2 input across all cortical

depths and WM, further compounding this reserve deficit. Under systemic hypoxia, young mice recapitulated the depth-dependent narrowing of the pO2 distribution seen in aging, but with further exacerbation: capillaries in deep layers and WM reached critically low pO_2 levels consistent with local hypoxia.
These findings establish 3PLM as a powerful tool for depth-resolved pO_2 imaging and reveal that deep cortical layers and WM face the greatest vulnerability to oxygen reserve deficits, with implications for understanding microvascular contributions to neurodegeneration.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.04/U13

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

Title: Neurovascular changes in DOCA-hypertension model in mice

Authors: R. IMMONEN[1], T. MIETTINEN[1], **J. RYTKÖNEN**[1], *K. LEHTIMÄKI[1], T. HUHTALA[1], Y. LI[2], J. C. DODGE[3];
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Abstract: Hypertension induces structural and functional changes in the brain, including changes in the blood vessels, neurons and their function. These alterations can lead to impaired cerebral blood flow, blood-brain-barrier disruption and ultimately increase the risk of vascular dementia and Alzheimer’s disease (AD). Deoxycorticosterone acetate (DOCA) is a mineralocorticoid that affects Renin-Angiotensin-Aldosterone system (RAAS). DOCA mimics effects of aldosterone leading to increased sodium reabsorption and excretion of potassium in the kidneys. Together with reduced kidney capacity and increased salt uptake it creates chronic hypertension mimicking neurovascular pathology seen in early vascular dementia. In this study the changes in neurovascular function were characterized using functional ultrasound (fUS) imaging in DOCA hypertension model.
The study was performed in adult female C57BL/6J mice. The hypertension model was induced with unilateral nephrectomy, s.c. deoxycorticosterone acetate (DOCA) pellet and excess sodium from drinking water (1% NaCl), w/v). The bodyweight and blood pressure of the animals was monitored. CINE MRI was utilized to evaluate the cardiac function and cardiac hypertrophy. Finally, fUS was performed for vascular reactivity and for perfusion response to somatosensory stimulation.
The DOCA-salt mice had reduced bodyweight compared to Sham group at weeks 2-5 after pellet implantation. Elevated blood pressure was observed in DOCA mice (SYS 140-150 mmHg) compared to sham operated animal (SYS approx. 120 mmHg). Hypertension was significant at

D7, D21, D28 and D35 after the DOCA pellet implantation and 1%-NaCl drinking water initiation. Heart rate during the BP measurement did not differ between DOCA and sham groups. A decreased response to Acetazolamide, a carbonic anhydrase inhibitor and a potent vasodilator, was detected with fUS imaging, indicating impaired vascular reactivity in DOCA mice. Decrease was significant in cortex and present as trend in hippocampus and thalamus. DOCA mice also showed decreased response to Whisker stimulation compared to Sham mice indicating functional hyperemia

Disclosures: R. Immonen: A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **T. Miettinen:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **J. Rytkönen:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **K. Lehtimäki:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **T. Huhtala:** A. Employment/Salary (full or part-time):; IQVIA Laboratories Finland Oy. **Y. Li:** A. Employment/Salary (full or part-time):; Sanofi. **J.C. Dodge:** A. Employment/Salary (full or part-time):; Sanofi.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.05/U14

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

Support: NIH Grant 5R01AG076625-04

Title: Graded Dietary Thiamine Insufficiency Stabilizes HIF-1α and Promotes Amyloid Accumulation in 3xTg-AD Mice

Authors: *B. BLACKBURN[1], S. BRANNEN[2], K. PRIEST[1], C. SHUPE[3], S. JAHAN[1], J. ZASTRE[1];
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Abstract: Alzheimer's disease (AD) patients frequently exhibit systemic thiamine (vitamin B1) insufficiency (TI). Thiamine is a cofactor for multiple enzymes involved in glucose metabolism, and TI is associated with cerebral glucose hypometabolism and cognitive decline in AD. Current animal models of TI rely on pyrithiamine (PT), a thiamine analog that induces acute thiamine deficiency and produces severe neuropathology and death within 10 days. This acute toxicity can mask the temporal onset of AD pathology and fails to represent the marginal TI observed clinically. Thiamine insufficiency stabilizes Hypoxia-Inducible Factor 1-alpha (HIF-1α), a transcription factor that drives downstream amyloidogenic and neurotoxic processes. However, these links were established only under severe PT-induced TI. Whether marginal dietary levels of TI relevant to AD are sufficient to stabilize HIF-1α and induce AD pathology remains unknown. We hypothesize that graded dietary TI is sufficient to stabilize HIF-1α and drive AD

pathology in a dose-dependent manner using 18-month 3xTg-AD mice. To address the shortcomings of current models, we developed a graded dietary TI model in which 18-month female 3xTg-AD mice were fed one of four diets: control (30 µg thiamine/day), minimum TI (1 µg), mild TI (0.1 µg), or complete thiamine deficiency (TD; 0 µg) (n=3-4/group). At 14 days, food intake and body weight were unchanged, confirming the absence of overt TI-associated symptomatology. Survival analysis revealed 100% mortality in the mild TI and complete TD groups and ~40% in the minimum TI group. Whole-brain Western blotting demonstrated a significant dose-dependent increase in HIF-1α stabilization compared with control. Soluble $A\beta_{1-42,}$ $A\beta_{1-40,}$ and Aβ42/40 ratio were all significantly elevated at mild TI and complete TD. Quantitative histomorphometry using Nissl staining revealed preserved neuronal density across the hippocampal, cortical, and thalamic regions. Soma circularity increased significantly, whereas eccentricity decreased significantly as TI severity increased. Together, these findings establish that dietary TI stabilizes HIF-1α and promotes AD pathology in a dose-dependent manner, with sustained insufficiency ultimately proving fatal. These results show that complete thiamine deficiency and thiamine analogs are not necessary to stabilize HIF-1α and promote AD pathology. Future studies will use the HIF-1α inhibitor YC-1 to test whether HIF-1α inhibition improves overall survival and attenuates amyloid accumulation and neuronal injury during graded TI, establishing HIF-1α as a potential therapeutic target.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.06/U15

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

Title: Interactive effects of high fat, high sugar diet with Alzheimer’s disease on hepatic oxidative stress and metabolism

Authors: *S. VARGHESE[1], C. M. LEVINE[2], C. CAGGIANO[2], C. M. MCCARTHY[3], W. ELAMAD[3], M. B. PARENT[2], R. G. FERESIN[3];
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Abstract: Objectives Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia in the aging population, disproportionately affecting women. Chronic consumption of a Western diet (WD) pattern, a high-fat, high-sugar diet (HFHS), is associated with increased AD risk. HFHS and AD have both been independently found to cause metabolic dysfunction in the liver; however, the extent to which AD and HFHS diet interact to compound hepatic dysfunction at the prodromal stage remains poorly understood. Thus, the objective of this study was to determine whether an AD-like genotype alters hepatic antioxidant and metabolic responses to HFHS feeding in female TgF344-AD rats during the

prodromal stage of disease development. Methods TgF344-AD and wildtype (WT) rats at 4.5 months of age were assigned to either continue standard chow (WT/chow; n = 5 or Tg/chow; n = 6) or switch to the HFHS diet (WT/HFHS n = 5 or Tg/HFHS; n = 6). Animals were matched for body weight within genotype and sex prior to diet assignment. Rats were euthanized 11 weeks later (7-7.5 months of age) corresponding to the prodromal stage of AD pathology in the TgF344-AD model. Liver tissue from female rats were collected for protein analyses via Western blot. Markers of antioxidative defense and metabolic signaling were assessed. Data were analyzed using two-way ANOVA. Results Hepatic superoxide dismutase (SOD) 2 was significantly higher in Tg/HFHS compared to WT/HFHS ($p = 0.03$). Glutathione peroxidase (GPX) 3 tended to be lower in Tg/HFHS compared to Tg/chow ($p = 0.06$). Catalase (CAT) expression was significantly lower in WT/HFHS rats compared with WT/chow rats ($p = 0.04$). Phosphorylated insulin receptor substrate 1 (p-IRS-1; serine 307) was lower in Tg/HFHS rats compared to WT/HFHS rats ($p = 0.007$), while phosphorylated extracellular signal-regulated kinase (pERK) tended to be higher ($p =0.09$). Conclusion Elevated hepatic SOD2 expression in Tg/HFHS rats suggests a selective mitochondrial antioxidant response to the combined challenges of AD pathology and HFHS feeding during prodromal stage. The absence of parallel changes in CAT and GPX3 indicates that this response may reflect compartment-specific adaptation rather than a global enhancement of antioxidant defense. Trends toward altered IRS1 and ERK signaling further suggest that AD-like genotype may modify hepatic metabolic responses to HFHS feeding. Additional studies examining inflammatory pathways and upstream signaling mechanisms are warranted to further characterize the hepatic consequences of AD pathology under obesogenic dietary conditions.

Disclosures: S. Varghese: None. **C.M. Levine:** None. **C. Caggiano:** None. **C.M. McCarthy:** None. **W. Elamad:** None. **M.B. Parent:** None. **R.G. Feresin:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.07/U16

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

Support: MRC grant MR/X003418/1

Title: Neurovascular and cognitive function in a tauopathy mouse model of dementia

Authors: *J. BERWICK[1], R. SIDHU[2], L. M. LEE[3], O. SHABIR[4], S. FRANCIS[2], C. HOWARTH[3];
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Abstract: Neurovascular coupling is the mechanism that regulates regional blood flow in the brain, ensuring adequate energy supply to active neurons. This mechanism links neuronal

activity to vessel constriction and dilation. The breakdown of neurovascular coupling is associated with the progression of neurodegenerative diseases, including Alzheimer's disease. This study aims to characterise cognitive and neurovascular function in a tauopathy mouse model of dementia, compared to wild-type counterparts. Experiments were undertaken on PS301S (PS19) TAU mice aged 7-10 months and WT littermates from both sexes. Novel object recognition (NOR) and the Barnes maze test (BMT) investigated memory deficits. Two-dimensional optical imaging spectroscopy was performed in awake, head-fixed mice to measure changes in cerebral blood volume (HbT), oxyhaemoglobin (HbO), and deoxyhaemoglobin (HbR) in the whisker barrel cortex in response to a 2s whisker stimulation in awake mice. Preliminary results indicate no differences in memory performance between the TAU and WT groups, as both show comparable memory outcomes in NOR and BMT. For NOR, both groups successfully performed the task, as the preference index for the novel object was above 50%. However, there were no significant differences between the groups in the preference index ($p=0.94$). For BMT, both groups show a similar time to escape the maze ($p=0.95$), time to locate the escape hole ($p=0.92$), and duration spent in the escape quadrant on probe day ($p=0.90$). However, the cortical haemodynamic responses to a 2s whisker stimulation show a significant reduction in TAU mice compared to WT. The peak HbT is significantly higher in WT than TAU mice across all trials (WT: n=29 sessions; TAU: n=37 sessions; $p=0.02$). Notably, TAU mice exhibit significantly more locomotion than WT mice during these imaging experiments. Preliminary results indicate impaired haemodynamic responses in TAU mice; however, baseline locomotion is significantly higher in TAU than in WT. Thus, locomotion could be a potential confounding factor. Ongoing cognitive assessments revealed no memory or behavioural deficits across groups, with all cohorts performing comparably on both NOR and BMT. Although this contrasts with prior literature, our preliminary findings suggest that such deficits may not be universal under the conditions tested.

Disclosures: J. Berwick: None. **R. Sidhu:** None. **L.M. Lee:** None. **O. Shabir:** None. **S. Francis:** None. **C. Howarth:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.08/U17

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

Title: Metabolic cognitive alterations are associated with memory dysfunction in older women with cognitive impairment

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Abstract: Alzheimers disease AD is the leading cause of dementia worldwide and is increasingly recognized as a systemic disorder in which metabolic dysfunction contributes to

neurodegeneration years before the onset of clinical symptoms. Although obesity and metabolic abnormalities have been associated with cognitive decline, their relationship with specific memory functions in older women remains poorly understood. The present study investigated whether cognitive impairment is accompanied by a distinct metabolic-cognitive phenotype characterized by alterations in body composition, metabolic profile, and memory performance. **Sixty three** elderly women aged 65 to 80 years were categorized based on their global cognitive performance scores according to Mini-Mental State Examination, comprising 31 women cognitively healthy and 32 women with cognitive impairment. **Anthropometric measurements, fasting biochemical analyses, and standardized neuropsychological assessments of episodic, verbal, visuospatial, and semantic memory were performed according to standardized protocols. Women with cognitive impairment exhibited significantly lower Mini-Mental State Examination scores, were older, had fewer years of education, and showed a less favorable metabolic profile, characterized by higher body mass index, waist circumference, tricipital skinfold thickness, fasting glucose, and triglyceride levels, together with reduced arm muscle area, compared with cognitively healthy women. They also demonstrated poorer performance across episodic, verbal, visuospatial, and semantic memory domains, with the most pronounced deficit observed in semantic memory.** These findings suggest a distinct metabolic cognitive phenotype associated with cognitive impairment in older women. The concurrence of increased adiposity, metabolic dysregulation, and memory deficits highlights a potential link between peripheral metabolic health and early neurodegenerative changes.

Disclosures: M.G. Guerrero Villalpando: None. **M. Solis-Ortiz:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.09/U18

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

Support: NIH Grant P20GM121307
AHA Grant 23CDA1051814

Title: Endothelial NOX1 Inhibition Attenuates Amyloid-β-Induced Blood-Brain Barrier Injury in Alzheimer’s Disease Models

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Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder affecting 7.4 million of Americans, with cerebrovascular dysfunction increasingly recognized as an early and critical component of disease progression. Oxidative stress links amyloid-β (Aβ) accumulation to blood-brain barrier (BBB) disruption and neurovascular injury. NADPH oxidase 1 (NOX1) is an important enzymatic source of reactive oxygen species (ROS) in brain endothelial cells and has

been implicated in Aβ-induced endothelial barrier dysfunction. However, the direct contribution of NOX1 to Aβ-induced endothelial oxidative stress and BBB injury remains incompletely characterized. Using mouse bEnd.3 and human hCMEC/D3 brain endothelial cells, we demonstrate that Aβ treatment increases ROS production in a dose-dependent manner and reduces expression of the critical components of BBB, tight-junction proteins claudin-5 and occludin. Pharmacologic inhibition of NOX1 with ML171 attenuated Aβ-induced ROS generation, with the strongest effect observed at 1 μM concentration. In parallel, endothelial NOX1 knockdown and systemic ML171 treatment in 3xTg-AD mice reduced vascular superoxide production and increased expression of the tight-junction protein ZO-1. Together, these findings suggest that endothelial NOX1 contributes to Aβ-induced oxidative stress and BBB dysfunction in AD. This work supports NOX1 as a potential therapeutic target for preserving cerebrovascular integrity and limiting neurovascular injury during AD progression.

Disclosures: M. Alam: None. **A. Toms:** None. **V. Tesic:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.10/U19

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

Title: HEPATIC OXIDATIVE STRESS IN A FEMALE ALZHEIMER'S DISEASE RAT MODEL FOLLOWING OVARIECTOMY

Authors: *W. ELAMAD[1], C. M. LEVINE[2], C. CAGGIANO[3], E. P. HARRIS[4], D. A. BANGASSER[2], M. B. PARENT[2], R. G. FERESIN[5];
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Abstract: Menopause is a recognized risk factor for Alzheimer's disease (AD), yet the hepatic consequences of ovarian hormone loss in this context remain poorly understood. Here, we investigated whether ovariectomy (OVX) and AD-like genotype interact to alter hepatic antioxidant defense and metabolic signaling. Female transgenic TgF344-AD rats (Tg; n=15) and wild-type controls (WT; n=14) underwent bilateral ovariectomy (OVX) or sham surgery at approximately 6.5 months of age and were euthanized 90 days post-surgery. Hepatic protein expression was assessed by western blot for nuclear factor erythroid 2-related factor (NRF)2-dependent and other antioxidant enzymes, including NAD(P)H quinone oxidoreductase (NQO)1, heme oxygenase (HO)-1, catalase (CAT), and superoxide dismutase (SOD)3, as well as the insulin signaling marker phosphorylated insulin receptor substrate 1 relative to total insulin receptor substrate 1 (p-IRS1/IRS1), and extracellular signal-regulated kinase 1/2 activation (p44/42). No significant effects of genotype, OVX, or their interaction were detected for NQO1, HO-1, CAT, SOD3, p-IRS1/IRS1, or p44/42 expression. Although not statistically significant, NQO1 expression tended to be higher in Tg-sham animals compared with WT-sham and Tg-

OVX groups, whereas HO-1 expression tended to be higher in Tg-OVX animals compared with Tg-sham and WT-OVX groups. CAT, SOD3, p-IRS1/IRS1, and p44/42 were comparable across all groups. Ovarian hormone loss for 90 days did not significantly alter hepatic antioxidant or metabolic signaling markers in TgF344-AD or WT rats under standard dietary conditions. While exploratory trends were observed in select NRF2-regulated proteins, additional studies with larger sample sizes and complementary inflammatory assessments are needed to determine whether AD pathology and ovarian hormone loss influence hepatic stress-response pathways.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.11/U20

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

Support: R01NS129407
R01NS133569
P30AG086404

Title: Glymphatic CSF influx and markers of Alzheimer’s

Authors: *A. VAKHTIN[1], H. LIN[3], N. SHAFF[2], S. M. HOBSON[4], L. H. O'CONNELL[1], D. COE[5], A. BIRG[3], E. ERHARDT[6], A. CAPRIHAN[2], S. G. RYMAN[7];
[1]The Mind Res. Network, Albuquerque, NM; [2]The Mind Res. Network, The Mind Research Network, NM; [3]New Mexico VA Hlth. Care Syst., Albuquerque, NM; [4]UNM Ctr. for Memory and Aging, Univ. of New Mexico / Ctr. for Memory and Aging, ALBUQUERQUE, NM; [5]Mind Res. Network, Albuquerque, NM; [6]Univ. of New Mexico, Albuquerque, NM; [7]Translational Neurosci., Mind Res. Network / Univ. of New Mexico, Albuquerque, NM

Abstract: The glymphatic system relies on infra-slow, rhythmic vasomotion to drive cerebrospinal fluid (CSF) through the perivascular and interstitial space in the brain - an important process that clears waste products from the central nervous system. While the glymphatic system is most active during sleep, our group has previously demonstrated that intermittent hypercapnia (IHC) can induce CSF dynamics in an awake state that closely mimic those observed during non-rapid eye movement (NREM) sleep. Importantly, this paradigm produced clearance of proteins and peptides implicated in Alzheimer’s disease and related dementias (ADRD) from the brain and into systemic circulation. In the interest of advancing IHC-induced CSF action as both a biomarker of glymphatic function in healthy individuals as well as a preventative intervention in early ADRD stages, we evaluated whether the magnitude of IHC-induced CSF inflow into the brain is associated with ADRD-related fluid markers in a group of individuals without diagnoses of Alzheimer's or related dementias (ADRD). The IHC

paradigm was administered during fMRI scans, and blood was collected from 61 non-ADRD individuals. During IHC, participants underwent 4 blocks of 35-second administration of 5% CO2 interleaved with 35 seconds of room air. The end-tidal CO2 (ETCO) time course was measured in the exhaled breath and used as a regressor to quantify the BOLD signal response to IHC in each participant. Consistent with prior publications, BOLD signal from the bottom slice of the 4th ventricle was used to quantify the CSF inflow, defined as the strength of ETCO-BOLD coupling at the optimal delay offset between the two time courses. Amyloid beta levels were below pathological levels in our participants and were found to be associated with CSF inflow magnitude during IHC. This finding underscores the important role that glymphatic dysfunction may play in early-stage neuropathology. The described IHC-induced CSF inflow paradigm can be a valuable tool for broad assessment of glymphatic health, impairment of which may serve as an early risk factor for the accumulation of ADRD-related proteins and peptides in the brain.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.12/U21

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

Support: Brains & Behavior (B&B) Seed Grant

Title: Lipids are increased in the dorsal hippocampus of TgF344-AD rats irrespective of diet-induced obesity

Authors: *T. M. BUCKNER, C. M. LEVINE, C. D. CAGGIANO, U. ZAFAR, V. NGO-VU, U. SIMAKOVA, M. B. PARENT;
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Abstract: Alzheimer’s disease (AD) represents 70% of dementia cases and is a leading cause of death in the world. AD pathology begins to accumulate during the asymptomatic preclinical period, with mild cognitive impairment marking the transition to prodromal AD. Neuropathology and cognitive decline worsen until dementia onset during the clinical period. Obesity is a significant risk factor for AD, nearly doubling risk and predicting more severe pathology. AD-related dysfunction in the dorsal hippocampus (dHC) worsens with age, contributing to memory loss as AD progresses. We previously reported that prodromal TgF344-AD (Tg) rats exhibit upregulated dHC cholesterol synthesis genes and that obesity downregulates lipid clearance pathways in the dHC. However, whether these changes in the expression of lipid-related genes are associated with an increase in lipids in dHC is not known. We hypothesized that chronic obesity during AD development increases dHC lipid accumulation and associates with worsened

dHC-dependent memory in Tg rats. To test this, we fed male and female wildtype (WT) and Tg rats a standard chow or high-fat, high-sugar (HFHS) diet from 5 to 14 months of age to induce obesity throughout AD progression (WT: n = 4 male, n = 6 female; Tg: n = 4 male, 5 female). We confirmed adiposity using EchoMRI, assessed spatial learning and memory using the Morris water maze (MWM), and visualized dHC lipid accumulation using filipin III histochemistry, which primarily labels cholesterol. The MWM results indicated that on the last day of acquisition, Tg rats traveled further than WT rats before reaching the platform ($F_{1,13} = 8.478$, $p = 0.012$) and there was a trend for Tg rats to spend less time in the target quadrant during the probe trial ($F_{1,13} = 4.562$, $p = 0.052$), suggestive of impaired spatial memory. Additionally, Tg rats displayed elevated filipin signal in dHC CA2 ($F_{1,13} = 6.189$, $p = 0.027$), CA3 ($F_{1,13} = 19.056$, $p = 7.65 \times 10^{-4}$), and dentate gyrus ($F_{1,13} = 84.185$, $p = 4.84 \times 10^{-7}$), suggesting that the Tg genotype potentiates hippocampal lipid dysregulation. Surprisingly, diet-induced obesity did not worsen dHC lipid accumulation or memory impairments as we have previously observed during the prodromal phase. These findings suggest that the Tg-induced increases in brain lipids occur during prodromal AD and persist until the clinical stage; whereas, the impact of diet-induced obesity may be transient.

Disclosures: T.M. Buckner: None. **C.M. Levine:** None. **C.D. Caggiano:** None. **U. Zafar:** None. **V. Ngo-Vu:** None. **U. Simakova:** None. **M.B. Parent:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.13/U22

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

Title: Characterization of new knock-in rat models for cerebral amyloid angiopathy in Alzheimer’s Disease

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Abstract: Cerebral amyloid angiopathy (CAA), resulting from the deposition of amyloid-β(Aβ) around the cerebral blood vessels, plays a major role in vasculardysfunction in Alzheimer’s disease (AD) and is observed in the majority of ADpatients. The CAA-associated pathologies include loss of smooth muscle cells,microhemorrhage, microinfarcts, inflammation, and motor impairments. However,the details of how CAA contributes to vascular dysfunction in AD are unclear, andthe absence of a suitable rodent model for CAA is a significant barrier tounraveling this puzzle. To study CAA-associated vasculopathy, severaltransgenic rodent models have been generated by random insertion of thehuman amyloid precursor protein (APP) gene with artificial promotor into thechromosomes, which is responsible for overproducing amyloid-β. However, thesetransgenic rodent models are not ideal, due to the artificial alteration of the gene-protein network. Therefore, we generated two knock-in rat models usingCRISPR-Cas9 technology: 1)

SIA-KI rat, which contains three APP mutations(Swedish, Iowa, Austria), known to enhance amyloid pathology, with thehumanized Ab sequence; and 2) Iowa-KI rat, which contains a single Iowamutation linked to severe CAA with the humanized Ab sequence. In this studyWe examined CAA pathology, neuroinflammation, and motor dysfunction in bothmodels. The SIA-KI rats showed significant Aβ plaque deposition and CAA inboth capillaries (type 1) and larger vessels (type 2) within the olfactory bulb,cortex, and thalamus, with an age-dependent increase. These rats also exhibitedpronounced neuroinflammation and progressive motor deficits, including gaitabnormalities and impaired coordination. In contrast, Iowa-KI rats showed noevidence of CAA pathology, neuroinflammation, and gait abnormalities, likelydue to possessing only one APP mutation compared to SIA-KI rats, whichharbored three APP mutations. Overall, the SIA-KI rat represents a promisingmodel for studying the mechanisms and pathophysiological consequences ofCAA in Alzheimer's disease.

Disclosures: A.B. Rizvi: None. **H. Ahn:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

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Program #/Poster #: PSTR049.14/U23

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01AG065345
R01NS134134
R01HL146574
R21AG091884
VCID-UMD-26-1514712
25POST1374445

Title: Loss of mural cell-derived laminin leads to microvascular dysfunction and cognition impairment

Authors: J. RUAN[1], A. NASROLLAHI[1], C. MARTIN[2], A. Y. SHIH[3], ***Y. YAO**[1];
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Abstract: Blood-brain barrier (BBB) damage is associated with lesion burden and cognitive dysfunction in cerebral small vessel disease (CSVD). Laminin, highly synthesized by mural cells in the brain, maintains BBB integrity. Accumulating evidence shows that laminin dysregulation correlates with CSVD. How it contributes to the pathogenesis of CSVD, however, remains unknown. To fill this gap in knowledge, we generated mutant mice with laminin deficiency in mural cells (PKO). The PKO mice exhibited age-dependent BBB disruption starting at middle age. Mechanistic studies revealed that both paracellular and transcellular mechanisms contributed to BBB injury. Additionally, PKO mice also demonstrated pericyte loss, basal

lamina thickening, and increased brain stiffness at middle age; and eventually developed compromised CSF influx/brain clearance, synaptic loss and cognitive impairment at old age. These results demonstrate that loss of mural cell-derived laminin induces vascular dysfunction, synaptic loss and cognitive impairment, highlighting a potential role of laminin dysregulation in the pathogenesis of CSVD.

Disclosures: J. Ruan: None. **A. Nasrollahi:** 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.; 25POST1374445. **C. Martin:** None. **A.Y. Shih:** None. **Y. Yao:** 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.; R01AG065345, R01NS134134, R01HL146574, R21AG091884, VCID-UMD-26-1514712.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.15/U24

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

Title: Cerebrovascular Endothelial FOXO1’s effect on Alzheimer’s Disease

Authors: C. NI[1], H. ZHU[1], Q.-F. CHEN[1], S. PAN[1], Y. ZHANG[2], ***W. SONG**[1]; [1]Wenzhou Med. Univ., Wenzhou, China; [2]Neurol., Drum Tower Hospital, Nanjing Univ., Nanjing, China

Abstract: Vascular dysfunction facilitates neurodegeneration and has been considered as one of earliest pathological changes in Alzheimer’s Disease (AD). FOXO1, a member of the FOXO (Forkhead Box O) transcription facto family, is a pro-longevity transcription factor. However, its role in AD remains poorly understood. We found that FOXO1 protein expression was significantly decreased in the cerebrospinal fluid and plasma of AD patients, as well as in the cerebral vascular endothelium of AD transgenic mice. Aβ reduced endothelial FOXO1 expression and enhanced its phosphorylation and acetylation, thereby inhibiting FOXO1 transcriptional activity. Inhibition of FOXO1 downregulated endothelial junctional and autophagy-lysosomal proteins, resulting in endothelial damages. Specific activation of FOXO1 in cerebrovascular endothelial cells mitigated endothelial and cerebrovascular dysfunction, and improved cognitive deficits in AD mice. Our study highlights the potential of targeting endothelial FOXO1 for the treatment of Alzheimer’s Disease.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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

Support: NIH Grant P30AG08404
NIH Grant P20AG068077
Beckman Institute at Caltech
Harvey Family Endowed Professorship at UNM

Title: Evidence for Nano Plastic Associations with Vascular Cognitive Impairment and Alzheimer's Disease in Human Brain

Authors: *E. L. BEARER[1,5], M. A. GARCIA[2], N. L. ADOLPHI[3], G. A. ROSENBERG[4]; [1]Univ. of New Mexico, Albuquerque, NM; [2]Col. of Pharm., Univ. of New Mexico, ALbuquerque, NM; [3]Biochem. and Mol. Biol., [4]NEUROLOGY, Univ. of New Mexico, Albuquerque, NM; [5]Bbe, Caltech, Pasadena, CA

Abstract: Environmental nano plastics are turning up in the human brain. We obtained post-mortem brain tissue from consented participants with Binswanger's or Alzheimer's disease. MRI-guided brain dissections were processed for histopathology. Perivascular glossy deposits testing negative for hemosiderin were observed. Methods: Tissue (~500 mg) adjacent to histologic blocks was harvested for pyrolysis gas chromatography/mass spectroscopy (py-GC/MS), KOH-digested, ethanol washed and pelleted by ultracentrifugation. Resultant pellets were subjected to three analyses: 1) Py-GC/MS; 2) TEM; 3) Laser-scanning confocal microscopy (LSM). For py-GC/MS, 1-3 mg of each pellet was run in sequence with calibration standards, brain storage buffer and true blanks. For TEM, resuspended pellets were either mounted on EM grids with or without negative stain, or embedded and thin-sectioned. For LSM, lambda scans of emission profiles were obtained from resuspended pellets, pure plastics from the industry and histologic brain sections. Results: By py-GC/MS polyethylene was found as well as 9 other plastic types. Quantification was not possible due to abundant lipids, including myelin, remaining in pellets as observed by TEM. Lipids have single bonded carbons as do plastics and thus many fragments cannot be differentiated by MS. Lambda scan emission profiles (424-695 nm) of particles in pellets found they fluoresced with the same unique profile as commercially available polyethylene, which had never seen human tissue. Glossy deposits in brain tissue displayed the same unique spectra as polyethylene and as the fluorescing particles in the "plastics-enriched" pellets which contain polyethylene by py-GC/MS. We found plastics embedded in the media of subcortical penetrating arterioles in Alzheimer's disease and in the adventitia of Binswanger's. Such particles were also found in choroid plexuses of both diseases, although different sizes, shapes and distributions. Nano-particles were abundant in brains from 2023-2024 but minimal in brains from 1960's; composed of different types of fluorescent particles in the same individual and between individuals (shapes, sizes, and emission spectra); primarily located in walls of blood vessels; and had no evidence of association with amyloid plaques or tau phosphorylation. Conclusion: Our technology reveals numerous aggregates of

plastic-like particles with unique hyperspectral profiles that mainly associate with subcortical white matter blood vessels. Heightened abundance around blood vessels suggests impact on vascular integrity with pathology from leakage or blockage, and increased risk of inflammation and hemorrhage.

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Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

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Program #/Poster #: PSTR049.17/U26

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

Support: 1R01AG081258-01A1
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1R01AG081874-01
26BTPA1622819
25CDA1453457
25POST1373581
26PRE1563496

Title: Sulfhydryl-Containing ACE Inhibitor Modulates Neurovascular Function in Alzheimer’s Disease

Authors: *D. J. SMITH, P. RODRIGUEZ, J. LANGMAN, C. T. CITADIN, J. ZACCARELLI MAGALHÃES, M. UDO, H. LIN;
Neurol., UTHealth Houston, Houston, TX

Abstract: Background: Alzheimer’s disease (AD) is the leading cause of dementia and is strongly associated with cerebrovascular dysfunction, including reduced cerebral blood flow, impaired neurovascular coupling, blood-brain barrier (BBB) disruption, and cognitive decline. Hypertension is highly prevalent in dementia patients and is commonly treated with angiotensin converting enzyme (ACE) inhibitors; however, whether ACE inhibitors are neuroprotective in AD remains unclear. Zofenopril is a lipophilic, BBB-permeable, sulfhydryl-containing ACE inhibitor capable of generating hydrogen sulfide (H_2S) independently of ACE inhibition. H_2S is a gasotransmitter that regulates vascular tone, neurotransmission, and cellular signaling. Given that H_2S production is largely established to be dysregulated in AD, we examined whether these deficits were consistent in the 3xTg-AD model and could be restored with zofenopril treatment. **Methods:** Aged 3xTg-AD and age/sex-matched C57BL/6J mice were treated with zofenopril or the non-sulfhydryl ACE inhibitor enalapril to distinguish H_2S-mediated effects from ACE inhibition. Cortical H_2S levels were measured by methylene blue assay. Neurovascular coupling, BBB leakage, and RBC speed was assessed using in vivo two-photon laser scanning microscopy

with FITC-dextran. Proteins were assessed by capillary-based immunoassay (ProteinSimple Jess™). Non-enzymatic H_2S release was determined by a DBrB based cell-free H_2S release assay. Blood pressure was measured via CODA® tail cuff measurement. Data was analyzed by unpaired t-test or one-way ANOVA with Tukey's post hoc test. **Results:** Aged 3xTg mice exhibited significantly reduced cortical H_2S levels compared to C57 controls ($p<0.05$). Zofenopril significantly increased cortical H_2S in 3xTg mice ($p<0.05$), whereas enalapril did not. Zofenopril was shown to release H_2S in a non-enzymatic fashion by the cell-free DBrB assay ($p<0.05$). Zofenopril and enalapril comparably reduced mean arterial blood pressure, as measured by tail-cuff ($p<0.05$). Aged female 3xTg mice showed impaired neurovascular coupling, shown by reduced whisker stimulation responses compared to C57 controls ($p<0.05$), with zofenopril treatment restoring vascular reactivity and increasing red blood cell velocity ($p<0.05$), while enalapril failed to produce neurovascular recovery. Zofenopril also significantly reduced BBB leakage and increased BBB-associated tight junction proteins ZO-1 and occludin in aged 3xTg mice ($p<0.05$). **Conclusion:** Zofenopril is able to release H_2S non-enzymatically and able to improve neurovascular function in the 3xTg-AD mouse model.

Disclosures: D.J. Smith: None. **P. Rodriguez:** None. **J. Langman:** None. **C.T. Citadin:** None. **J. Zaccarelli Magalhães:** None. **M. Udo:** None. **H. Lin:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.18/U27

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

Support: SECIHTI Grant 847273

Title: Phenylbutyrate Enhances Recognition Memory and Dendritic Spine Density in the Prefrontal Cortex and Hippocampus of Hypertensive Female Rats

Authors: *L. AGUILAR HERNÁNDEZ[1], M. GOMEZ-VILLALOBOS[2], E. BALTAZAR-GAYTAN[3], G. FLORES[4], J. MORALES-MEDINA[1];
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Abstract: Hypertension and aging are among the most prevalent health challenges worldwide and commonly occur together. This comorbidity is associated with neuronal alterations that contribute to cognitive decline and may be exacerbated by chronic hypertension. In this study, middle-aged female spontaneously hypertensive (SH) rats were used as a translational model to investigate the combined effects of hypertension and aging on brain function and structure. We

evaluated the impact of phenylbutyrate (PB), a compound with reported neuroprotective and anti-inflammatory properties, on recognition memory and dendritic spine morphology. Our results show that PB-treated animals exhibited significant improvements in both short- and long-term recognition memory, as determined by the novel object recognition task. Morphological analyses revealed that PB increased dendritic spine density in the prefrontal cortex (PFC) and throughout the dorsal hippocampus, including the CA1, CA3, and dentate gyrus (DG) regions. In addition, PB promoted the prevalence of mature spine types, increasing the proportion of mushroom and bifurcated spines in the PFC and hippocampal subregions analyzed. Collectively, these findings demonstrate that PB ameliorates recognition memory deficits while preserving dendritic spine density and promoting structural maturation within cortico-hippocampal networks in hypertensive middle-aged female rats. These results highlight the therapeutic potential of PB for addressing neurocognitive dysfunction associated with the coexistence of hypertension and aging.

Disclosures: L. Aguilar Hernández: None. **M. Gomez-Villalobos:** None. **E. Baltazar-Gaytan:** None. **G. Flores:** None. **J. Morales-Medina:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.19/U28

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

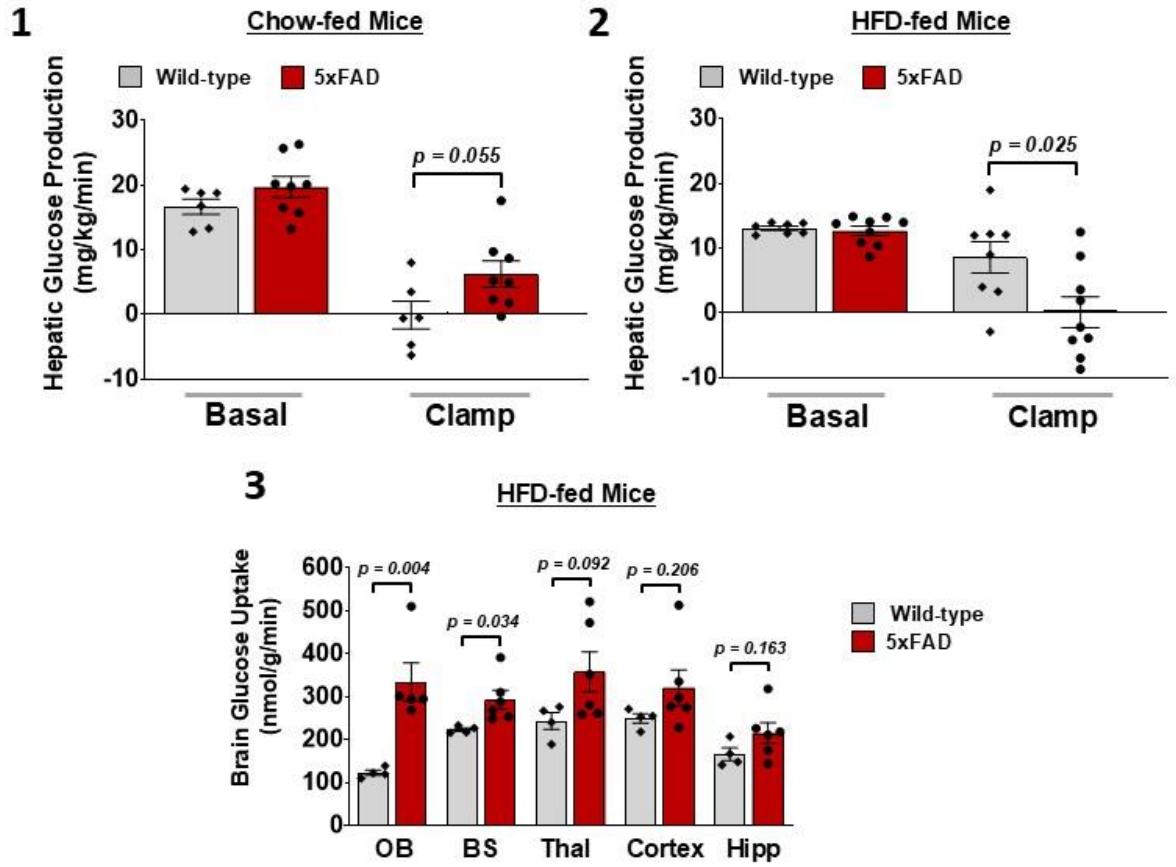
Support: National Institutes of Health R01-AG085308

Title: 5xFAD Mice Develop Altered Glucose Metabolism and Insulin Action in the Brain and the Liver After a High-Fat Diet

Authors: *A. D. DARYANANI, G. HUR, M. SAJID, H. CHOI, J. BOWMAN, F. SOTE, F. HUSSAIN, A. JAYAMOHAN, D. DAVIS-ANAGBOSO, A. MUÑOZ, H. D'URSO, M. CUNNINGHAM, C. KIM, L. MBENGUE, L. TAUER, P. MANN, J. K. KIM;
Mol. Med., UMass Chan Med. Sch., Worcester, MA

Abstract: Obesity and insulin resistance are major risk factors for Alzheimer's disease (AD), and over 80% of individuals with AD have type 2 diabetes. Yet, the connection between AD and insulin resistance remains poorly understood. Male 5xFAD and wild-type (WT) mice were fed high-fat diet (HFD; 60% fat by calories) (n=8~11/group) or chow diet (n=6~8/group) starting at 6~9 weeks of age. We performed a hyperinsulinemic-euglycemic clamp with ^{3}H-glucose infusion to measure insulin action and glucose metabolism in awake mice. On chow diet, hepatic glucose production (HGP) during clamp increased in 5xFAD compared to WT, indicating impaired insulin action in the 5xFAD liver (Fig. 1). Whole-body glucose turnover did not differ between groups, indicating preserved peripheral insulin sensitivity in 5xFAD (43.0 vs 42.5 mg/kg/min in WT). After 4 months of HFD, both groups became obese with similar body

weights (HFD: 37.2 vs 41.7 g; chow: 25.9 vs. 28.6 g in 5xFAD and WT, respectively). Fat mass decreased by 13% in 5xFAD after HFD (18.3g vs 21.1g in WT). During clamp, HFD-fed 5xFAD showed a reciprocal change in liver glucose metabolism, with reduced HGP compared to WT (Fig. 2). Insulin completely suppressed HGP in 5xFAD, indicating rescue from diet-induced insulin resistance in the liver. Whole-body glucose turnover increased by 16% in HFD-fed 5xFAD (22.0 vs 18.9 mg/kg/min in WT). We used a bolus of ^{14}C-2-deoxyglucose (non-metabolizable glucose analog) to measure brain glucose uptake. Glucose metabolism in the olfactory bulb increased 2.7-fold in 5xFAD compared to WT after HFD (Fig. 3). 5xFAD mice exhibited higher glucose uptake in the brain stem (31%) and thalamus (47%), with similar trends in the cortex and hippocampus (Fig. 3). Overall, 5xFAD showed reduced insulin sensitivity in the liver on chow diet but were protected from HFD-induced insulin resistance, with increased glucose metabolism in most brain regions after HFD. Our findings indicate that diet-induced obesity in 5xFAD paradoxically enhances insulin sensitivity in the liver possibly as an adaptive response to dysregulated brain glucose metabolism.



Disclosures: A.D. Daryanani: None. **G. Hur:** None. **M. Sajid:** None. **J. Bowman:** None. **L. Tauer:** None. **J.K. Kim:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.20/U29

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

Support: TREAT-AD #U54AG065181
Indiana Biosciences Research Institute

Title: Evaluating the metabolic effects of the GLP-1 receptor agonist semaglutide in a rodent model of Alzheimer's disease

Authors: M. M. SPICER[1], ***C. A. MAHLER**[1], B. J. LORENTZ[1], S. A. MOWERY[1], C. INGRAHAM[2], C. R. RANGEL-BARAJAS[3], P. J. KNERR[1], T. I. RICHARDSON[3,1], A. L. OBLAK[3], J. A. KULAS[1], J. DOUROS[1];
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Abstract: Epidemiologic, real-world evidence and early-stage clinical trials indicate that glucagon-like peptide 1 receptor (GLP-1R) agonists reduced the incidence of dementia. However, recent late-stage clinical trials of semaglutide in patients with established, but early Alzheimer's disease (AD) such as EVOKE/EVOKE+, have yielded equivocal results. This underscores a critical need to better define the mechanisms by which GLP-1R signaling influences neurodegenerative processes to help identify patient populations that may be best served by GLP-1R agonist therapy. Here, we examine the effects of GLP-1R agonism on metabolic and neurodegenerative features of AD using wild-type (WT) and hAβ-SAA (AD) mice. Male and female mice (N = 12/sex) were characterized longitudinally from 8 to 32 weeks of age under chow-fed and high-fat diet (HFD) conditions. Metabolic assessments included glucose (GTT), mixed meal (MMTT), and insulin tolerance test (ITT), as well as energetic assessments via TSE metabolic cages. Following 14 weeks of HFD exposure after metabolic reassessment, mice were assigned to either vehicle, semaglutide or weight-matched control groups, enabling distinction of pharmacological effects from those attributable to weight loss alone prior to tissue collection. Our data demonstrate a notable improvement in glucose control and protection from diet-induced obesity in female, but not male, AD mice compared to WT controls, suggesting possible improvements in endogenous GLP-1R tone and α- to β-cell paracrine communication. Semaglutide treatment induced robust weight loss across all genotypes and sexes, with male AD mice demonstrating a greater response than their WT counterparts. Weight reduction was likely driven by loss of adipose tissue, but unlike the males, both female WT and female AD semaglutide treated and weight matched mice did not experience a significant lean mass loss compared to controls. Together, these findings identify a previously unrecognized, sex-dependent metabolic phenotype in hAβ-SAA mice and suggest that AD-associated biology may influence responsiveness to GLP-1R manipulation. Furthermore, our work establishes and characterizes a preclinical neurometabolic model that supports mechanistic evaluation of GLP-1R agonism and future incretin-based strategies for AD.

Disclosures: M.M. Spicer: None. **C.A. Mahler:** None. **B.J. Lorentz:** None. **S.A. Mowery:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly & Co. (unrelated). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Volari Therapeutics (unrelated). **C. Ingraham:** None. **C.R. Rangel-Barajas:** None. **P.J. Knerr:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly & Co. (unrelated). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Volari Therapeutics (unrelated). **T.I. Richardson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Monument Biosciences (unrelated), Candenza (unrelated). **A.L. Oblak:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Monument Biosciences (unrelated). **J.A. Kulas:** None. **J. Douros:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly & Co. (unrelated). E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Volari Therapeutics (unrelated).

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.21/U30

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

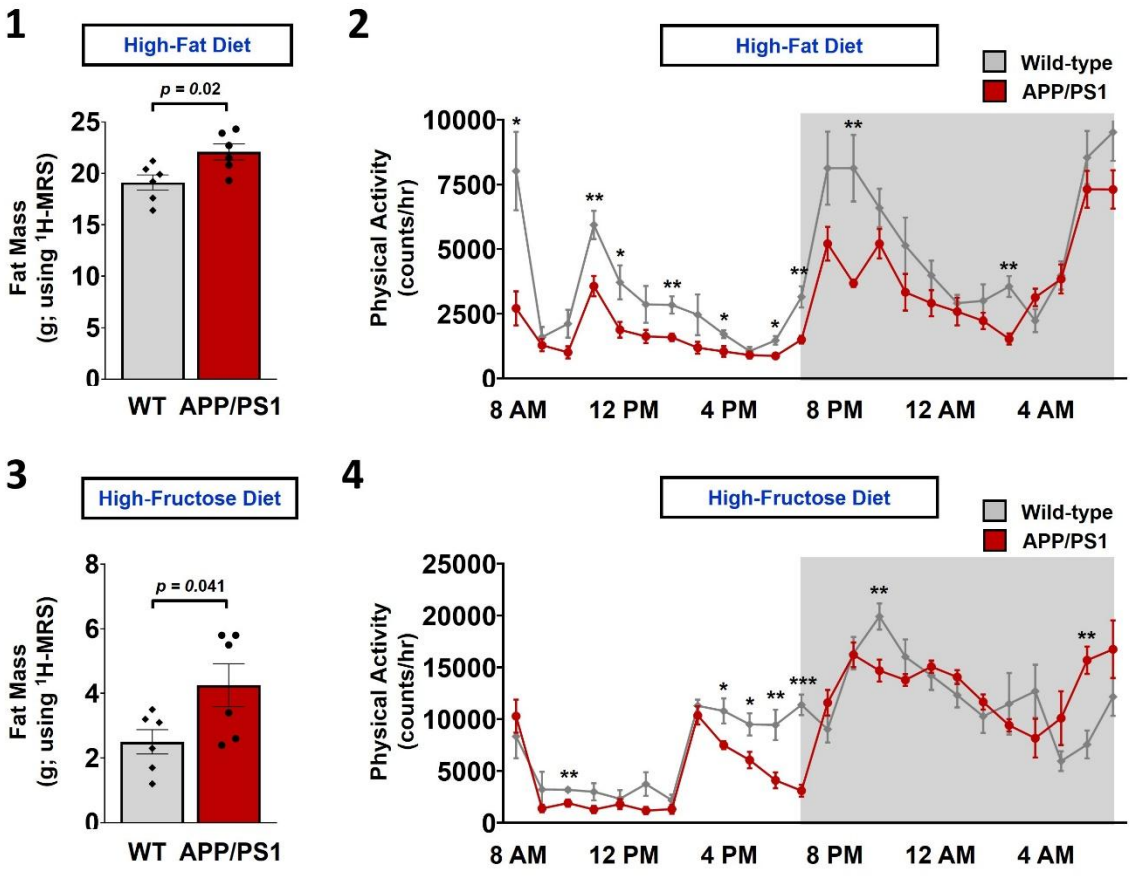
Support: National Institutes of Health R01-AG085308

Title: APP/PS1 Mice Develop Increased Obesity After High-fat Diet or High-fructose Diet Due to Reduced Physical Activity

Authors: *G. HUR, A. DARYANANI, M. SAJID, J. KINGHAM, S. HAARALA, H. D'URSO, F. HUSSAIN, P. MANN, L. TAUER, J. BOWMAN, J. K. KIM;
Mol. Med., UMass Chan Med. Sch., Worcester, MA

Abstract: Diets play a key role in modulating Alzheimer's disease (AD) risk, but the relationship with pathogenesis is unclear. American diets high in fat and high-fructose corn syrup contribute primarily to obesity and metabolic diseases. Here, we examined the effects of high-fat diet (HFD; 60% kcal fat) on energy balance in male APP/PS1 and wild-type (WT) littermates starting at 2 months of age (n=6/group). After 4 months of HFD, both groups became profoundly obese compared to chow-fed mice (51.2±1.5g in APP/PS1 vs. 49.5±0.9g in WT, compared to

~32g in chow-fed mice). We used ^{1}H-magnetic resonance spectroscopy to measure whole-body fat and lean mass. Fat mass increased by 16% in APP/PS1 compared to WT after HFD whereas lean mass did not differ (Fig. 1). Using metabolic cages to assess energy balance, we found a 35% decrease in physical activity (PA) in APP/PS1 compared to WT (Fig. 2). O_2 consumption and CO_2 production rates also decreased by ~5% at nighttime in APP/PS1 (150±2 ml/hr vs. 156±3 ml/hr in WT for VO_2, p=0.050; 111±2 ml/hr vs. 117±3 ml/hr in WT for VCO_2; p=0.031). In contrast, daily food intake did not differ (1.4±0.1g in APP/PS1 vs. 1.7±0.3g in WT). Next, we examined the effects of high-fructose diet (HFrD; 67% kcal fructose) on energy balance in APP/PS1 and WT starting at 4 months of age (n=6/group). While body weights did not differ (28.1±1.2g in APP/PS1 vs. 26.8±0.9g in WT), fat mass increased by 72% in APP/PS1 compared to WT (Fig. 3). Similar to HFD effects, PA decreased mostly at daytime in APP/PS1 compared to WT (Fig. 4). Interestingly, 24-hour O_2 consumption increased by 10% in APP/PS1 (110±2 ml/hr vs. 100±3 ml/hr in WT; p=0.001). 24-hour CO_2 production also increased by 9% in APP/PS1 (97±2 ml/hr vs. 89±3 ml/hr in WT; p=0.001). Daily food intake did not differ. In conclusion, APP/PS1 were more susceptible to diet-induced obesity after HFD or HFrD primarily due to reduced PA. Differential effects of HFD and HFrD on energy expenditure rates suggest complex adaptive response in energy balance in APP/PS1, supporting an important role of dietary fat and fructose content in the pathogenesis of AD.



Disclosures: G. Hur: None. **A. Daryanani:** None. **M. Sajid:** None. **J. Kingham:** None. **S. Haarala:** None. **H. D'Urso:** None. **F. Hussain:** None. **P. Mann:** None. **L. Tauer:** None. **J. Bowman:** None. **J.K. Kim:** None.

Poster

PSTR049: Alzheimer's Disease: Blood Flow and Metabolism

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR049.22/U31

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

Support: ZIA-ES103310

Title: Defining Bioenergetic Stress-Induced Cholinergic Neurodegeneration in Mice: Molecular and Phenotypic Characterization

Authors: *S. SAHA[1], A. PAPANERI[1], W. GLADWELL[2], D. SPINA[3], L. R. WILSON[1], J. D. CUSHMAN[1], G. CUI[1];
[1]Neurobio., [2]Mol. And Cell. Biol., NIH/NIEHS, Research Triangle Park, NC; [3]Bio-Rad Laboratories, Inc., Hercules, CA

Abstract: Optimal mitochondrial bioenergetic balance is essential for neuronal function and overall brain health. Impaired energy production or utilization in the brain, referred to as bioenergetic stress, is primarily driven by mitochondrial dysfunction and is increasingly recognized as an early contributor to numerous neurodegenerative disorders, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), both of which are associated with cholinergic neuron (CN) degeneration. Mitochondrial transcription factor A (Tfam) is critical for maintaining mitochondrial DNA integrity, regulating oxidative stress, and preserving mitochondrial function, thus playing indispensable roles in regulating cellular bioenergetics. To investigate the direct contribution of bioenergetic stress in cholinergic neurodegeneration, we generated a cholinergic neuron-specific Tfam knockout mouse model (ChAT-cre;Tfam-/-, abbreviated as ChTf) and characterized its molecular and phenotypic consequences. ChTf mice exhibited progressive mitochondrial dysfunction and age-dependent loss of cholinergic neurons. Compared with littermate controls, knockout mice showed a marked decline in body weight beginning at 13.5 weeks of age. By 16 weeks, mice developed a stooped posture and reduced mobility, consistent with declining neuromuscular function. Behavioral analyses revealed decreased exploratory activity and locomotion in the Phenotyper assay, as well as impaired motor performance and coordination on the rotarod. Histological analyses using choline acetyltransferase (ChAT) immunostaining further demonstrated age-dependent degeneration of basal forebrain cholinergic neurons and striatal cholinergic interneurons. To investigate molecular alterations associated with cholinergic neurodegeneration, we developed a multiplex Droplet Digital™ PCR (ddPCR™) assay (Bio-Rad Laboratories) and quantified expression of neurodegeneration-related genes, including APP and ChAT, in knockout and control mice. Ongoing studies include spinal cord histopathology and in vivo fiber photometry using ATP and

cholinergic fluorescent sensors to evaluate bioenergetic dynamics across multiple brain regions. Collectively, these findings demonstrate that Tfam deletion-induced bioenergetic stress in cholinergic neurons leads to progressive neurodegeneration and movement impairments. This novel model provides a valuable platform for investigating mechanisms of cholinergic neuron disease and identifies disrupted bioenergetics as a potential driver and therapeutic target of cholinergic neurodegeneration.

Disclosures: S. Saha: None. **A. Papaneri:** None. **W. Gladwell:** None. **D. Spina:** None. **L.R. Wilson:** None. **J.D. Cushman:** None. **G. Cui:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.01/U32

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

Support: 1R03AG091250-01

Title: Tracking Synaptic Autophagy: How Amyloid-Beta Pathogenesis Alters Presynaptic Cargo Capture and AV Maturation

Authors: *P. BISHT, H. GROSSO JASUTKAR;
Dept. of Neurol., Rutgers Robert Wood Johnson Med. School, Rutgers Univ., Piscataway, NJ

Abstract: The homeostatic pathway macroautophagy, herein referred to as autophagy, is implicated in both synaptic function and Alzheimer's disease (AD) pathogenesis. From a disease perspective, several lines of evidence from post-mortem human brain studies and animal models suggest that autophagy plays a role in neurodegenerative disorders such as AD, raising the possibility that autophagy is a therapeutic target for disease modification. However, prior efforts to modulate autophagy for neuroprotection have had mixed results. To modulate autophagy effectively, it is necessary to better understand how it is affected in the disease state. Therefore, we aimed to identify the step in autophagic processing of synaptic proteins that is impacted by AD-associated pathogenesis. To address this, primary hippocampal neuronal cultures were generated from $APP^{NL\text{-}F/NL\text{-}F}$ knock-in (APP KI) mice expressing GFP-tagged LC3. These mice express a mutated form of humanized amyloid precursor protein, which is cleaved to produce the disease-associated protein amyloid-beta (Aβ). At 16 days *in vitro* (DIV), after synaptic maturation, cultures were transduced with AAV constructs expressing the presynaptic proteins Vamp2, Vglut, or Snap25 tagged with mCherry. Subsequently, immunofluorescence microscopy was used to evaluate the colocalization of these proteins with AVs to determine if pathogenic Aβ interferes with capture of these presynaptic proteins into AVs. To investigate whether AD-associated pathogenesis also interferes with AV maturation, primary hippocampal cultures from APP KI mice were transduced at DIV16 with an AAV-RFP-GFP-LC3 construct that expresses LC3 tagged with RFP and GFP. In this system, immature AVs are labelled with both GFP and

RFP, whereas upon maturation and acidification, GFP fluorescence is quenched, leaving only the RFP signal. For the imaging, we used confocal microscopy at DIV 18 to assess the relative maturity of AVs in APP KI cultures compared with wild type controls. Collectively, these studies provide mechanistic insights into autophagy dysfunction in AD and identify potential therapeutic targets for preserving synaptic integrity and neuronal health.

Disclosures: P. Bisht: None. **H. Grosso Jasutkar:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.02/V1

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

Support: Cure Alzheimer's Fund
NIH Grant GM122523
NIH Grant NS120725

Title: Calcium/Calmodulin-Dependent Protein Kinase II is a Major Target of Enhanced Protein Kinase C Activity in Neurodegeneration

Authors: *O. BHATTACHARYA[1], C. CHANG[2], N. C. SHANER[3], T. YARON-BARIR[4], J. L. JOHNSON[4], S. MEHTA[2], J. ZHANG[2], L. CANTLEY[5], A. NEWTON[2];
[1]UCSD Dept. of Pharmaology, La Jolla, CA; [2]Dept. of Pharmacol., [3]Dept. of Neurosciences, UC San Diego, La Jolla, CA; [4]Dana-Farber Cancer Inst., Boston, MA; [5]Dept. of Cell Biol., Harvard Med. Sch., Cambridge, MA

Abstract: Protein kinase C (PKC) plays an important role in the brain, where it regulates receptor trafficking, neurotransmission, and cytoskeletal dynamics. Aberrantly high activity of Ca^{2+}-dependent PKC isozymes is associated with neurodegenerative disorders including Alzheimer's disease (AD), where PKCα activity is enhanced, and Spinocerebellar Ataxia Type 14 (SCA14), where PKCγ has high basal activity. However the mechanism by which hyperactive PKC drives neurodegeneration remains unclear. Here, we identify Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), a family of serine/threonine kinases that regulate synapse structure and function, as a major target of PKC in both these neurodegenerative diseases. Specifically, substrate motif analysis of phosphoproteomic data sets from brain or cerebellum of mice harboring either an AD-associated mutation in PKCα (M489V) or SCA14-associated mutation in PKCγ (ΔF48) reveal enhanced phosphorylation of CaMKII substrates. Western blot analysis of brain or cerebellum from these mice models confirmed elevated phosphorylation of CaMKII at the autophosphorylation site, Thr286, a marker for its activation. To investigate the mechanism by which PKC regulates CaMKII, we used live-cell imaging where genetically encoded reporters for PKC (C Kinase Activity Reporter 2 or CKAR2) and either CaMKII (CaMKII Kinase Activity Reporter or CaMKAR) or a Ca^{2+} indicator (Cameleon) were expressed in the same cell. These

fluorescence resonance energy transfer (FRET)-based reporters undergo stimulus-dependent conformational changes that alter energy transfer between their corresponding fluorophores. Treatment of HEK293T cells with thapsigargin, a SERCA pump inhibitor that elevates intracellular Ca^{2+} levels, resulted in a robust increase in Ca^{2+} levels and corresponding increase in CaMKII activity. Pretreatment of cells with the PKC inhibitor Gö6983 abolished PKC activity and also reduced CaMKII activity. These results identify CaMKII as a downstream target of PKC signaling and provide new insight into the mechanisms by which aberrant PKC may contribute to neurodegeneration in both AD and SCA14.

Disclosures: O. Bhattacharya: None. **C. Chang:** None. **N.C. Shaner:** None. **T. Yaron-Barir:** None. **J.L. Johnson:** None. **S. Mehta:** None. **J. Zhang:** None. **L. Cantley:** None. **A. Newton:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.03/V2

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

Support: JSPS KAKENHI Grant Number JP22K11305, JP19K11362, JP16K12944
Grant number JPJ013268 from the Acquisition, Technology & Logistics Agency(ATLA)

Title: Voluntary exercise restores dopamine D4 receptor expression and synaptic plasticity through a transcriptional regulatory mechanism in a mouse model expressing amyloid β oligomers

Authors: *T. OCHIISHI[1], K. HIRANO[2], K. KIYOSUE[3], M. KAKU[4];
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Abstract: It is well known that habitual physical exercise improves cognitive function. Exercise is therefore attracting attention as a potential preventive and new therapeutic intervention for dementia. However, molecular mechanisms underlying exercise-induced recovery remains unclear. In Alzheimer’s disease (AD), memory impairment occurs prior to the formation of amyloid plaques and neuronal loss. Recent studies suggest that this impairment may be caused by intracellular amyloid-β (Aβ) oligomers. We have developed a transgenic mouse model (Aβ-GFP Tg mouse) that expresses a fusion protein of Aβ and GFP, which forms only low-molecular-weight Aβ oligomers exclusively within neurons. This model does not exhibit amyloid plaque formation, neurofibrillary tangles, or brain atrophy, but shows cognitive impairment, reduced long-term potentiation (LTP), altered spine morphology, and oxidative stress from 2-3months of age. Therefore, this model mouse is specifically designed for analyzing

the toxicity of Aβ oligomers in the early stages of AD. Voluntary exercise on a running wheel for more than 7 weeks improved memory deficits in Aβ-GFP Tg mice. Exercise also activated Wnt signaling pathway. Concurrently, dopamine D4 receptor (DRD4) expression, which was significantly reduced in non exercise Aβ-GFP Tg mice relative to wild-type, was restored by exercise at both mRNA and protein levels. In hippocampal slices, a DRD4 agonist improved LTP impairment in Aβ-GFP Tg mice. Therefore, we investigated the mechanism by which increased DRD4 expression contributes to the cognitive improvements observed in this model following exercise. Mass spectrometry analyses revealed that CCAAT/enhancer-binding protein α (C/EBPα), a candidate transcriptional factor of DRD4, might bind to Aβ oligomer. Chromatin immunoprecipitation demonstrated enrichment of C/EBPα at the DRD4 promoter and C/EBPα overexpression induced DRD4 expression, suggesting that C/EBPα positively regulates DRD4 transcription. In a C/EBPα-responsive luciferase assay, Aβ-GFP suppressed C/EBPα expression, whereas CHIR, a GSK3β inhibitor, enhanced C/EBPα expression and reversed the suppression caused by Aβ-GFP. These findings suggest that exercise restores DRD4 expression and synaptic plasticity in Aβ pathology via a C/EBPα-dependent transcriptional mechanism sensitive to Wnt/GSK3β.

Disclosures: T. Ochiishi: None. **K. Hirano:** None. **K. Kiyosue:** None. **M. Kaku:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.04/V3

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

Support: NIH Grant UL1 TR002535
NIH Grant AG072102
Boettcher Foundation
Colorado State University College of Veterinary Medicine and Biomedical Sciences

Title: Co-activation of selective nicotinic acetylcholine receptor subtypes is required to reverse hippocampal network dysfunction, fear memory loss, and amyloid pathology in Alzheimer's disease

Authors: *R. LEE[1], H. KIM[1], E. BLACK[1], S. KIM[2];
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Abstract: Alzheimer's disease (AD) is the most common form of dementia with no known cause and cure. Research suggests that a reduction of GABAergic inhibitory interneurons' activity in the hippocampus by beta-amyloid peptide (Aβ) is a crucial trigger for amyloid pathology and cognitive impairment in AD via hyperexcitability. Therefore, enhancing hippocampal inhibition is thought to be protective against AD. However, hippocampal inhibitory cells are highly diverse,

and these distinct interneuron subtypes differentially regulate hippocampal inhibitory circuits and cognitive processes. Moreover, Aβ unlikely affects all subtypes of inhibitory interneurons in the hippocampus equally. Hence, identifying the affected interneuron subtypes in AD to enhance hippocampal inhibition optimally is conceptually and practically challenging. We have previously found that Aβ selectively binds to two of the three major hippocampal nicotinic acetylcholine receptor (nAChR) subtypes, α7- and α4β2-nAChRs, but not α3β4-nAChRs, and inhibits these two receptors in cultured hippocampal inhibitory interneurons to decrease their activity, leading to hyperexcitation in excitatory neurons. We have also revealed that co-activation of α7- and α4β2-nAChRs is required to reverse the Aβ-induced adverse effects in hippocampal excitatory neurons. Here, we discover that α7- and α4β2-nAChRs predominantly control the nicotinic cholinergic signaling and neuronal activity in hippocampal parvalbumin-positive (PV+) and somatostatin-positive (SST+) inhibitory interneurons, respectively. Furthermore, we reveal that co-activation of these receptors is necessary to reverse hippocampal network dysfunction, amyloid pathology, and fear memory loss in the amyloid pathology model mice. This suggests that co-activation of PV+ and SST+ cells via stimulating α7- and α4β2-nAChRs together is a novel strategy for neuroprotection against AD.

Disclosures: R. Lee: None. **H. Kim:** None. **E. Black:** None. **S. Kim:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.05/V4

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

Support: AHA Grant 26PRE1563496
NIH Grant 1R01AG081258-01A1
NIH Grant 1RF1NS132291-01
NIH Grant 1R01AG081874-01

Title: Dopamine D2 Receptor Signaling as a Therapeutic Target in Alzheimer's Disease

Authors: *J. LANGMAN, J. ZACCARELLI MAGALHÃES, M. UDO, D. J. SMITH, B. BRITO NANNI, P. RODRIGUEZ, C. T. CITADIN, H. LIN;
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Abstract: Alzheimer’s Disease (AD) is the leading type of dementia that is affecting over 55 million people worldwide. While amyloid-β and tau pathologies have long dominated AD research, recent findings highlight cerebral blood flow dysregulation and neurovascular dysfunction as early contributors to AD pathogenesis. These vascular abnormalities contribute to blood brain barrier breakdown, neuroinflammation, and cognitive decline, also known as vascular contributions to impairment and dementia (VCID). Dopamine and its receptors, particularly the D2 receptor (D2R), have been implicated in cerebrovascular regulation.

Although little is known about D2R signaling in the context of VCID, D2R is highly prevalent in the brain. The goal of this study was to determine whether pharmacological activation of D2R can mitigate AD-induced neurovascular and behavioral dysfunction in the 3xTg-AD mouse model. Neurovascular coupling and blood-brain barrier integrity were assessed *in vivo* using two-photon microscopy. Tight junction proteins were quantified using capillary immunoassay ProteinSimple JESS. Cognitive and affective behaviors were measured using Y-maze, open field, novel object recognition test and forced swim test. Preliminary findings suggest that D2R activation improves neurovascular coupling via increase in % change in diameter following whisker stimulation, blood-brain barrier integrity via increase in tight junction proteins and decrease in fluorescence in perivascular space and functional outcomes in 9-12 months 3xTg-AD mice. Collectively, this work establishes a mechanistic link between D2R signaling and cerebrovascular regulation in AD and insights into how D2R activation influences blood-brain barrier integrity, neurovascular coupling and behavioral outcomes.

Disclosures: J. Langman: None. **J. Zaccarelli Magalhães:** None. **M. Udo:** None. **D.J. Smith:** None. **B. Brito Nanni:** None. **P. Rodriguez:** None. **C.T. Citadin:** None. **H. Lin:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.06/V5

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

Support: R01AG092683
R61AG094667

Title: Partial reduction of GIRK1 rescues interneuron function and reduces network hypersynchrony in an Alzheimer’s disease mouse model

Authors: *C. CHEN[1], K. MA[2], J. SHIN[3], J. HERBERT[4], Y. ZHANG[4], K. SHEN[5], I. SÁNCHEZ-RODRÍGUEZ[6], J. D. NAVARRO-LOPEZ[7], J. J. PALOP[8];
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Abstract: Neuronal hyperexcitability is an early feature of Alzheimer’s disease (AD) that contributes to network dysfunction. GIRK channels, key regulators of neuronal excitability, have been implicated in this process. Lhx6-expressing interneurons, including PV and SST cells, play a crucial role in maintaining network synchrony, and their dysfunction is associated with hypersynchrony, spontaneous epileptiform discharges, and reduced gamma oscillations in mouse models of AD. Here, we investigated the role of GIRK channels in Lhx6 interneuron activity and

their contribution to AD-related hyperexcitability.RNA-sequencing analysis revealed an interneuron-selective upregulation of the GIRK1 subunit (Kcnj3) in Lhx6 interneurons in J20 mice, and this upregulation was part of a hub gene network associated with impaired cognitive performance. Because GIRK channels suppress neuronal excitability, we hypothesized that elevated GIRK1 expression in interneurons may contribute to reduced interneuron excitability, network hypersynchrony, and memory impairment in AD. To test this hypothesis, we partially reduced GIRK1 levels in Lhx6 interneurons in Lhx6-Cre;GIRK1-flox+/−;J20 mice and assessed ex vivo oscillatory activity using optogenetic stimulation at different frequencies, hippocampal excitability through input/output (I/O) curves, synaptic plasticity via long-term potentiation (LTP) at the CA3-CA1 synapse, in vivo electrophysiological recordings, and cognitive function.Our results show that selective GIRK1 deletion in Lhx6 interneurons increased the intrinsic excitability of inhibitory interneurons, enhanced firing output, and facilitated the induction of gamma oscillations, indicating that this manipulation increases interneuron excitability. In the J20 AD model, this approach rescued hippocampal long-term potentiation (LTP) deficits and counteracted hyperexcitability. Partial GIRK1 ablation also reduced epileptiform spike activity and improved memory performance in J20 mice. These findings establish a critical role for GIRK1 channels in Lhx6 interneurons in AD-related network dysfunction. Targeting GIRK1 in these cells may represent a promising therapeutic strategy to increase interneuron excitability and mitigate hyperexcitability and cognitive impairment in AD.

Disclosures: C. Chen: None. **K. Ma:** None. **J. Shin:** None. **J. Herbert:** None. **Y. Zhang:** None. **K. Shen:** None. **I. Sánchez-Rodríguez:** None. **J.D. Navarro-Lopez:** None. **J.J. Palop:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.07/V6

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

Support: CIHR PJT 186196

Title: Characterizing age-, sex-, and subregion-specific differences of NMDAR mislocalization in the 3xTg mouse model of Alzheimer’s disease

Authors: *C. CONNORS[1], F. ASHRAFGANJOIE[1], M. P. PARSONS[2];
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Abstract: Synaptic NMDA receptors (NMDARs)— linked to cell survival— contain more GluN2A subunits, while extrasynaptic NMDARs— associated with excitotoxicity—contain more GluN2B. Mislocalization of NMDARs from synaptic to extrasynaptic sites occurs in Alzheimer’s disease (AD), but how this varies across hippocampal subregions, sexes, and ages

remains unclear. As many traditional methods cannot directly visualize NMDARs in intact tissue, this study used high-resolution Airyscan imaging to quantify GluN2A and GluN2B puncta density, localization, and volume across hippocampal subregions at presymptomatic and symptomatic stages in the 3xTg AD mouse model in both sexes.
In both the hippocampal CA3 and dentate gyrus (DG) regions, genotype-dependent differences in NMDAR mislocalization were significantly more pronounced at symptomatic stages versus presymptomatic stages, suggesting NMDAR mislocalization progresses with time. Furthermore, in symptomatic 3xTg mice, alterations in both nonsynaptic NMDAR density and subunit-specific puncta volume were observed in region- and sex-dependent patterns. For example, the CA3 showed a female-specific decrease in nonsynaptic density with increased volume, whereas the DG showed a male-specific increase in density with reduced volume.
Together, these findings demonstrate complex age-, sex-, and hippocampal subregion-specific differences in NMDAR mislocalization in the 3xTg mouse model, providing a foundation for assessing therapies aimed at restoring NMDAR localization.

Disclosures: C. Connors: None. **F. Ashrafganjoie:** None. **M.P. Parsons:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.08/V7

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

Support: Centre for Brain Research core grant
CSIR fellowship to Nimisha Basavaraju : 09/1233(13189)/2022-EMR-I

Title: Wnt/β-catenin signaling dysregulation in Alzheimer's disease

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Abstract: Wnt signaling is a pathway critical to synapse as its activation results in synaptic protein recruitment. Given that synapse loss is an early characteristic feature of Alzheimer’s disease, understanding Wnt signaling dysregulation becomes important due to its role in influencing synaptic activity. Previous studies have focused on co-receptor Lrp5/6, kinase Gsk3β and antagonist Dkk1 while β-catenin, the central molecule of the signaling, remains poorly characterized with respect to dysregulation of Wnt signaling in AD. Our study aims to identify dysregulation of β-catenin with respect to its phosphorylation and ubiquitination, processes that are vital for signal activation, in AD. Given this, we evaluated phosphorylation and ubiquitination of β-catenin in 9-month-old wild type and APP/PS1 mice through immunoblot analysis which showed a significant decrease in APP/PS1 suggesting a decreased degradation leading to increased signal activation. However, our transcription target analysis through qPCR in APP/PS1 showed significant decrease suggesting a downregulated Wnt signaling. This

suggests a dysregulation of Wnt signaling due to impairment of β-catenin post translational modifications. Therefore, targeting these post translational modifications of β-catenin for therapeutic strategies could be vital in restoring Wnt signaling, thereby also contributing to synapse maintenance in AD.

Disclosures: N. Basavaraju: None. **R. Kommaddi:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

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Program #/Poster #: PSTR050.09/V8

Topic:

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Title: NRN1 is a synaptic target for resilience to Alzheimer’s disease

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Abstract: Synaptic resilience enables some individuals to maintain cognitive function despite substantial Alzheimer’s disease (AD) pathology. NRN1 was identified as a synaptic protein associated with cognitive resilience to AD pathology through integration of human proteomic, neuropathological, and functional connectivity data. Multiplex tandem mass tag mass spectrometry was performed on postmortem human brain tissue spanning normal aging, asymptomatic AD, and symptomatic AD cases. Protein co-expression network analyses were integrated with dendritic spine morphometry to examine relationships between protein expression and spine density. NRN1 expression correlated with higher dendritic spine density, consistent with a potential role in synaptic maintenance. In a separate cohort of Religious Order Study Memory Religious Orders Study and Memory and Aging Project (ROSMAP) participants, higher NRN1 protein abundance was associated with higher global cognition, episodic memory, semantic memory, and working memory. NRN1 levels were significantly reduced in AD and

inversely correlated with neurofibrillary tangle burden and Braak stage. Single-nucleus transcriptomic data showed decreased NRN1 expression in glutamatergic neurons with advanced disease progression. Together, these findings support NRN1 as a synaptic protein associated with cognitive resilience and dendritic spine integrity in AD. We hypothesize that NRN1 has therapeutic potential to preserve synaptic function in patients at risk for developing AD.

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Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.10/V9

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

Support: Robert J. and Nancy D. Carney Institute for Brain Science

Title: Effects of Amyloid Beta on Presynaptic Complexin Expression

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Abstract: Loss of synaptic integrity is a key feature of Alzheimer's disease (AD) and understanding mechanisms of synaptic loss can improve AD diagnostics and therapeutics. Complexins are a family of presynaptic proteins that bind to the trans-SNARE complex to modulate SNARE-mediated neurotransmitter release. Altered expression of complexins 1 and 2 has been observed in a range of neurological conditions. Previous work has indicated that complexins associate with cognitive function, with complexin 1 and 2 linked to early and late-stage disease progression, respectively. Immunohistochemical analysis of post-mortem human brain has shown low overlap between complexins and amyloid beta (Aβ+) plaques. A plasma proteomic screen in participants along the AD continuum by our lab identified complexins 1 and 2 as the most significantly associated plasma proteins with established AD blood biomarkers, with plasma levels increasing with advancing AD neuropathology. In the current study, we aim to evaluate the expression of complexins in response to Aβ. Using *in vitro* neuronal cell models treated with increasing doses of oligomeric Aβ42 (oAβ42; 0.01 μM, 0.05 μM, 0.1 μM, vehicle control) for 20 hours, we find an increase in CPLX expression in response to oAβ42; such that there is a significant difference between vehicle- and high dose-treated cells (One-way ANOVA with Tukey's multiple comparisons test; $P = 0.031$). In parallel, immunohistochemistry analysis of 5xFAD transgenic AD mice demonstrated frank reductions of CPLX1 and CPLX2 in peri-Aβ plaque regions throughout the cerebral cortex and hippocampus. These results validate the need for further research into the Aβ-driven pathological changes in complexins observed in AD and support their potential as diagnostic and therapeutic targets.

Disclosures: T.A. Ihejirika: None. **J.H. Mendiola:** None. **E.N. Wilson:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.11/V10

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

Title: Effects of amyloid-β oligomer on pre- and postsynaptic neuronal responses induced by local acetylcholine stimulation of cholinergic synapses in Aplysia feeding neural circuit

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Abstract: Amyloid-β (1-42) oligomers (o-Aβ) are causative agents of Alzheimer's disease that impair signaling via synaptic dysfunction. In *Aplysia kurodai,* we previously found that IPSPs in jaw-closing motor neurons (JC) evoked by cholinergic multi-action neurons (MA) in the buccal ganglia were rapidly inhibited by o-Aβ (1 μM). Acetylcholine (ACh) receptors in this synapse are nicotinic, and chloride ion channels are involved. In this study, to investigate how o-Aβ acts on the cholinergic synapses, ACh was iontophoretically applied using micropipettes to two regions of buccal ganglia: one containing only postsynaptic receptors (JC cell body) and the other containing synaptic binding sites (neuropil). ACh stimulation of JC cell bodies induced JC hyperpolarization and o-Aβ (1 μM) inhibited the responses with a significant delay (40~50 min) after application. We searched for specific neuropil regions (SNRs) where ACh stimulation induced some responses in JC and MA simultaneously because previous reports predicted feedback of ACh release at presynaptic terminals. ACh stimulation mostly induced JC hyperpolarization and MA depolarization, both blocked by curare. And it was found that o-Aβ inhibited both JC and MA responses immediately after application. We further decreased synaptic transmission using two types of solutions (HMLC and HMLC-Na) to eliminate presynaptic effects. Both solutions quadrupled Mg^{2+} concentration, halved Ca^{2+} concentration compared to seawater, and adjusted Na^{+} concentration to maintain osmotic pressure. HMLC maintained Cl^{-} concentration, while HMLC-Na minimized decrease in Na^{+} concentration. In HMLC, JC hyperpolarization induced by stimulation of SNRs was reduced, but JC hyperpolarization induced by stimulation of neuropil regions that elicit only JC responses remained unchanged. Furthermore, HMLC sometimes changed small MA depolarizations into hyperpolarization, which was thought to be due to a decrease in depolarization caused by low Na+ concentration in this solution. Therefore, our observed MA depolarization may be a mixture of depolarization and hyperpolarization. We explored o-Aβ effects on MA and JC responses induced by stimulation of SNRs in HMLC-Na. o-Aβ inhibited MA depolarization immediately after application, while inhibited JC hyperpolarization with a significant delay. These results suggest that the rapid o-Aβ inhibition of JC hyperpolarization induced by stimulation of SNRs may be caused by inhibition of ACh release at presynaptic terminals due to rapid inhibition of

MA depolarization, followed by the delayed o-Aβ inhibition of postsynaptic receptor-mediated JC hyperpolarization.

Disclosures: T. Nagahama: None. **S. Nagahama:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

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

Support: the Research Grants Council of Hong Kong (the General Research Fund HKUST16102824)
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the SIAT–HKUST Joint Laboratory for Brain Science (Joint Laboratory Funding Scheme [JLFS/M-604/24])

Title: Discovery of Nell-1 as a Key Regulator of Hippocampal Synaptogenesis

Authors: *Y. ZHOU[1,2], X. YANG[1,2], H. UHM[1,2], W.-Y. FU[1,2], Y. JIANG[1,2], A.-Y. FU[1,2,3], N. Y. IP[1,2,3];
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Abstract: Proteomic profiling of plasma from individuals with Alzheimer’s disease (AD) revealed dysregulation of blood proteins associated with multiple biological pathways, including neurodegeneration, suggesting that blood-based protein biomarkers may reflect neurodegenerative processes. Among the dysregulated proteins, NELL-1 (neural epidermal growth factor-like 1), a neuronally enriched secreted factor, was downregulated in AD patient plasma. Moreover, during aging and AD progression, plasma NELL-1 levels were negatively associated with plasma neurofilament light chain level, a marker of neurodegeneration, further supporting plasma NELL-1 level is associated with neurodegeneration. To investigate whether and how *NELL1* is involved in neuronal functions, we examined its expression and role in hippocampal neurons. In the adult mouse hippocampus, Nell-1 is predominantly expressed in excitatory neurons and enriched in the postsynaptic density fraction, suggesting a role of Nell-1 in synaptic function. Treatment of cultured hippocampal neurons with recombinant Nell-1 increased excitatory synapse density, as indicated by elevated pre- and postsynaptic puncta and their colocalization. Proteomic profiling of Nell-1-treated hippocampal neurons further revealed

an increased levels of proteins associated with dendrite morphogenesis and glutamate transport. Together, these findings identify Nell-1 as a synaptic organizer that promotes presynaptic and postsynaptic development in hippocampal neurons and suggest that decreased Nell-1 levels may contribute to synaptic dysfunction and neurodegeneration in AD.

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Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

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

Support: NIA R00 AG078501

Title: Investigating endosomal regulation of hippocampal-dependent memory in an Alzheimer's Disease model

Authors: *E. B. WRIGHT, B. CONNELL, P. BHUIYAN, A. A. KEISER;
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Abstract: Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with disrupted endosomal trafficking and altered signaling pathways, including Transforming Growth Factor-β (TGF-β). Canonical TGF-β signaling requires coordinated receptor activation, internalization, endosomal trafficking, and downstream SMAD-mediated transcription. Evidence from AD mouse models and patient tissue indicates that impaired SMAD2/3 signaling may contribute to disease progression, as demonstrated by cytoplasmic mislocalization of phosphorylated SMAD2/3 and reduced nuclear signaling. We previously identified the Type I TGF-β receptor ACVR1C as a bidirectional regulator of hippocampus-dependent memory. Expression of *Acvr1c* is significantly reduced in aging and 5xFAD mouse hippocampus, and Acvr1c overexpression in the dorsal hippocampus improves cognitive performance in both aging and AD mouse models. However, the mechanisms by which endosomal trafficking regulates ACVR1C signaling during memory consolidation, and the ways in which these processes are altered in AD, remain unclear. To investigate endosomal regulation of ACVR1C under physiological and AD conditions, dorsal hippocampus (dHPC) tissue was collected from 4-5-month-old 5xFAD and age-matched wild-type mice following a 10-minute Object Location Memory (OLM) acquisition task. The tissue was processed for immunostaining and protein analyses. Immunofluorescence was used to assess ACVR1C colocalization with markers of distinct endosomal compartments, including Rab5 (early endosomes), Rab7 (late endosomes), Rab11 (recycling endosomes), and LAMP1/Cathepsin D(lysosomes), in dHPC sections. Co-immunoprecipitation assays were conducted to evaluate interactions between ACVR1C and Type II receptors (ACVR2A, ACVR2B, and BMPR2) during memory consolidation. Future

ELISA-based analyses will assess SMAD phosphorylation in wild-type and 5xFAD mice to determine whether downstream SMAD2/3 activation is altered in AD. Collectively, these studies will define how endosomal trafficking influences ACVR1C receptor dynamics during hippocampus-dependent memory consolidation and provide a framework for understanding how disruptions in receptor trafficking may contribute to memory impairment in AD.

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Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

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Program #/Poster #: PSTR050.14/V13

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

Support: RO3 AG083563

Title: Identification Of Novel C1q-Interacting Proteins That Mediate Synaptic Recruitment in Alzheimer's Disease

Authors: *H. KHAN;
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Abstract: The pathological correlate most tightly associated with cognitive decline in Alzheimer’s disease (AD) is synapse loss, yet mechanisms mediating synaptic loss in AD remain unclear. Within the brain, activated complement proteins coats the outer membrane of weak/damaged synapses, tagging synapses for phagocytic pruning by microglia. This process is tightly regulated to prevent aberrant synaptic pruning. For example, complement C1q (the activating molecule of the classical pathway) coordinates complement labeling of synapses by depositing on the outer membrane of weak/damaged synapses. However, the exact mechanisms enabling C1q to tag certain synapses for pruning while leaving other synapses intact remain unknown. We hypothesize that AD affected synapses display C1q binding partners that mediate C1q synaptic deposition. To identify disease specific binding partners that facilitate C1q synaptic deposition in the context of AD, we immunoprecipitated (IP’d) C1q from postmortem AD, mild cognitive impairment (MCI) and cognitively unimpaired frontal cortex tissue and used unbiased mass spectrometry to identify proteins that Co-IP with C1q. Proteins identified through mass spectrometry were compared between groups to identify disease stage specific C1q synaptic binding proteins and subsequently analyzed for their ability to augment complement activation using *in vitro* assays. We identified multiple novel C1q-interacting partners spanning diverse biological pathways, suggesting that synaptic C1q interacting proteins may regulate synaptic removal and complement activation in AD. Future studies will investigate how these C1q interacting proteins are altered over AD progression and determine if restoring C1q regulation protects synapses from AD pathology. Understanding these interactions may provide new

insights into disease pathogenesis and identify potential therapeutic targets to mitigate synapse loss and cognitive decline.

Disclosures: H. Khan: A. Employment/Salary (full or part-time):; Michigan State University.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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

Support: NIH Grant NS123050

Title: Amyloid Beta's Long-Term Plasticity Disruption Mechanism is Initiated by the Modification of Phosphorylation of Cav1.2 on S1928

Authors: *A. F. NISAN[1], S. ROUGE[4], P. BARTELS[4], Z. ZENG[2], R. BERUMEN[2], M. TORRES FLORES[3], J. A. GRAY[3], M. C. HORNE[5], J. W. HELL[6];
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Abstract: Amyloid beta's (Aβ) plaque formation and accumulation is the hallmark of Alzheimer's disease (AD). The synaptotoxic and plasticity impairment effects of Aβ are well documented. However, Aβ's ability to form multiple oligomeric peptide species and bind diverse channels and receptors has made pinpointing its precise post-synaptic neurotoxic mechanism(s) a persistent challenge. Aβ binds to and stimulates the β_2 Adrenergic receptor (β_2AR). β_2AR forms a localized signaling complex with L-type Ca^{2+} channel (LTCC) $Ca_V1.2$, the trimeric Gαs protein, adenylyl cyclase (AC), and the cAMP-dependent protein kinase (PKA). β_2AR's physical association with $Ca_V1.2$ is required for $Ca_V1.2$'s activity up-regulation upon β_2AR stimulation. More recent work has demonstrated that Aβ's binding to β_2AR increases the phosphorylation of S1928 the PKA phosphorylation site on the c-terminal of Cav1.2, and thus upregulates channel activity. Ca^{2+} signaling has long been highlighted as having an important role in the etiology of AD as well as other forms of dementia. To further tease out the exact initial steps in Aβ's synaptic plasticity disruption mechanism, we used B6/129 or S1928A KI mice ages P60-P90 to prepare 400μM coronal hippocampal slices using a vibratome. A bipolar electrode was placed in the *stratum radiatum* of the CA1 region to stimulate the Schaffer collaterals. Evoked field EPSPs (fEPSPs) were recorded in the *stratum radiatum*. Average slope of evoked fEPSPs 50 minutes post-LTP induction were used for statistical comparisons to baseline responses and analyzed using a one-way ANOVA or unpaired t-test. Our current results support a long-standing hypothesis that Aβ impairs hippocampal neural network dynamics by disrupting long-term synaptic potentiation (LTP) and tips the balance of plasticity towards long-term synaptic depression (LTD). We demonstrate the initial steps of Aβ long-term synaptic plasticity

impairment mechanism occur via its signaling through the β_2AR-Ca$_V$1.2 complex. Acutely displacing β_2AR from Ca$_V$1.2 using a calcium channel c-terminal mimic peptide, in the presence of Aβ restores LTP. Acute inhibition of S1928 phosphorylation by displacing $\beta_2$2AR in wildtype mouse slices as well as chronic genetic disruption of S1928 phosphorylation in S1928A KI mice prevents Aβ's LTP impairment. Aβ's ability to induce LTD is also prevented in slices of S1938A KI mice. Our results center the β_2AR-Ca$_V$1.2 complex and S1928 phosphorylation site as a high potential therapeutic target in AD drug development.

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Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.16/V15

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

Support: R01AG075440 6
1RF1AG07425

Title: Single Molecule Super Resolution Imaging Uncovers Profound Excitatory Synapse Loss in Hippocampal CA1 Region of 5xFAD Alzheimer's Model

Authors: *P. M. MANDHYAN, L. N. MADHU, T. CHATTERJEE, A. K. SHETTY;
Cell Biol. and Genet., Texas A&M Univ., College Station, TX

Abstract: Cognitive decline in mid and advanced-stage Alzheimer's disease (AD) is linked to the collapse of synaptic networks. Within hippocampal memory circuits, excitatory synapses are a compelling first target because their degeneration can weaken CA1 circuit throughput, cause an excitatory-inhibitory imbalance, and lead to hippocampus-dependent cognitive decline. However, individual synapses in the brain are defined by nanoscale apposition between presynaptic and postsynaptic proteins, a relationship that is difficult to discern accurately with conventional confocal microscopy of immunofluorescence-processed brain sections. We therefore developed a single-molecule super-resolution workflow to first quantify excitatory synapse loss. We measured the density of excitatory synapses in the CA1 stratum radiatum (CA1-SR) of 11-month-old 5xFAD and age-matched naive control mice. Free-floating 30 μm-thick brain tissue sections through the hippocampus were processed for dual immunofluorescence using primary antibodies against vesicular glutamate transporter 1 (VGLUT1) and Homer 1, proteins found respectively in pre- and post-synaptic membranes of excitatory synapses. We carried out direct stochastic optical reconstruction microscopy (dSTORM) on a Bruker Vutara platform, using single-molecule localization to reconstruct nanoscale coordinate maps of synaptic protein organization beyond the diffraction limit. Sparse

fluorophore emission events were localized across thousands of frames, allowing marker organization to be analyzed as spatial coordinates rather than diffraction-limited puncta. We used a custom MATLAB-based marker-pairing pipeline to detect spatial apposition between presynaptic and postsynaptic marker clusters and calculate synapse density from reconstructed CA1-SR images. This coordinate-based strategy reduces reliance on manual puncta counting and supports reproducible comparison of synapses across groups. We find that excitatory synapse density is reduced by 65.2% in the CA1-SR of male 5xFAD mice compared with age-matched naive male mice (Naive: 0.601 ± 0.046; 5xFAD: 0.209 ± 0.015; mean ± SEM, n=5 animals/group; $p<0.01$). We are now applying this pipeline to quantify inhibitory synapse density using antibodies against the vesicular GABA transporter (VGAT) and gephyrin to ascertain changes in the excitatory-to-inhibitory synapse ratio in 5xFAD mice. The results suggest profound excitatory synapse loss in hippocampal CA1-SR as a sensitive quantitative readout during the advanced stage of AD and establish a scalable dSTORM- and MATLAB-based platform for mapping subtype-specific synapse loss in AD models.

Disclosures: P.M. Mandhyan: None. **L.N. Madhu:** None. **T. Chatterjee:** None. **A.K. Shetty:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.17/V16

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

Support: HMH start up funding

Title: Early Excitation-Inhibition Imbalance and aberrant excitability in LC noradrenergic neurons precedes neurodegeneration in Alzheimer’s disease

Authors: *B. ZHAO[1], J. LI[2];
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Abstract: Alzheimer’s disease (AD) is a multifactorial neurodegenerative disorder strongly associated with aging and characterized by complex pathophysiological mechanisms. Notably, specific neuronal populations within the neocortex and brainstem, including the locus coeruleus (LC), exhibit heightened vulnerability during the earliest stages of the disease. One early hallmark of AD is neuronal hyperexcitability, which may contribute to synaptic dysfunction, neuropsychiatric symptoms, and cognitive decline. In this study, we hypothesize that early hyperexcitability in vulnerable neuronal populations, particularly within the LC, arises from AD-related disruptions in glutamatergic neurotransmission and synaptic integrity. To test this hypothesis, we examined the electrophysiological and synaptic properties of noradrenergic LC neurons in 3xTg-AD mice at 2, 4 and 6 months of age, representing early stages of AD

pathology. Whole-cell patch-clamp recordings revealed a significant increase in spontaneous firing activity despite a reduction in spontaneous and miniature excitatory postsynaptic current frequency (sEPSC/mEPSC). In contrast, spontaneous and miniature inhibitory postsynaptic current(sIPSC/mIPSC) frequencies were significantly increased. Paired-pulse ratio analysis indicated impaired presynaptic glutamate release probability. Consistent with these functional alterations, immunohistochemical analysis revealed a reduction in VGLUT2-positive excitatory puncta and an increase in VGAT-positive inhibitory puncta surrounding LC neurons, while TH-positive neuronal number remained unchanged. In addition, preliminary analyses suggest alterations in membrane conductances associated with neuronal excitability, including voltage-gated K^+ currents and hyperpolarization-activated cyclic nucleotide-gated (HCN) channel function. Together, these findings demonstrate that LC neurons undergo early synaptic remodeling characterized by reduced glutamatergic and enhanced GABAergic input prior to neurodegeneration. The dissociation between spontaneous firing and evoked firing reveals a decoupling of intrinsic pacemaker activity from stimulus-evoked excitability. These alterations may represent an early circuit-level substrate underlying LC vulnerability and neuropsychiatric symptoms in AD.
Key words: Alzheimer's disease; locus coeruleus; electrophysiology; excitability

Disclosures: B. Zhao: None. **J. Li:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.18/V17

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

Support: NIH NIA R03AG093239

Title: Investigating the role of dendritic mitochondria in CA2-specific Alzheimer's disease pathology

Authors: *M. ALSALMAN, L. TURNER, S. A. SWANGER, S. FARRIS;
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Abstract: The entorhinal cortex (EC) to hippocampus circuit is one of the first to be affected by Alzheimer's disease (AD)-related pathology. While EC input forms synapses onto the distal dendrites of each hippocampal CA subregion (CA1, CA2, CA3), it is unclear whether each subregion is similarly impacted by AD pathology. Synapses require metabolic support from mitochondria and dendritic mitochondrial fragmentation is detected in AD model (J20) mice before amyloid-beta (Aβ) plaque deposition. Evidence from AD mouse models show mitochondrial calcium overload exacerbates Aβ plaque pathology. Specifically, genetic deletion of the mitochondrial calcium uniporter (MCU), the main route of calcium influx into the matrix, prevents Aβ plaque pathology in AD mice. CA2 distal dendrites harbor larger mitochondria that

are enriched for MCU relative to CA1. Further, mitochondrial matrix calcium levels are higher in CA2 distal dendrites relative to proximal dendrites, an effect not found in CA1. Thus, we hypothesized that elevated mitochondrial calcium levels in CA2 distal dendrites should result in increased Aβ plaque deposition.
In aged J20 mice, we found subregion- and dendritic layer-specific differences in total Aβ staining (two-way ANOVA, main effect of layer, $p=0.0013$; subregion, $p=0.0034$; interaction, $p=0.0009$; N=5 mice, both sexes, 16+ months). Specifically, CA1 cell bodies had lower levels of Aβ compared to CA2 (Tukey's $p<0.0001$) and CA3 ($p<0.0001$) cell bodies. In distal dendrites, CA2 had the highest Aβ levels compared to CA1 ($p=0.0089$) and CA3 ($p=0.0008$). Thus, consistent with our hypothesis, the dendritic domains with the highest mitochondrial calcium levels showed the most Aβ plaque deposition. If EC-CA2 synapses are more vulnerable to Aβ pathology, then we expect them to have increased Aβ levels before neighboring subregions. In 6-month-old J20 mice and littermate controls, Aβ immunostaining generally showed minimal Aβ plaques. Qualitatively, in CA2 cell bodies, Aβ was higher than in CA1 cell bodies, similar to aged J20 mice. These data suggest that CA2 neurons express higher levels of Aβ prior to plaque pathology, suggesting they may be more vulnerable. Ongoing studies are comparing dendritic mitochondrial morphology and matrix calcium levels between genotypes to determine whether dysregulation of mitochondrial calcium signaling in CA2 distal dendrites is associated with the higher Aβ plaque burden. Defining the mechanisms underlying EC-hippocampal circuit vulnerability is necessary for understanding how AD memory impairment develops and for identifying therapeutic targets to prevent synapse loss.

Disclosures: M. Alsalman: None. **L. Turner:** None. **S.A. Swanger:** None. **S. Farris:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.19/V18

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

Support: NIH Grant R21AG085379
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Title: Synaptic Proteomic Networks Reveal Protein Targets Related to Tau Seeds in Alzheimer's Disease

Authors: *E. HOBBY[1], D. A. BENNETT[3], N. T. SEYFRIED[4], J. H. HERSKOWITZ[2]; [2]Neurol., [1]Univ. of Alabama at Birmingham, Birmingham, AL; [3]Rush Alzheimer's Dis. Ctr., Rush Univ. Med. Ctr., Chicago, IL; [4]Human Genet., Emory Univ., Atlanta, GA

Abstract: Proteomic studies can generate robust assessments that examine changes in protein abundances across different disease conditions, such as Alzheimer's disease (AD). These analyses can provide lists of various molecules altered in AD; however, identifying the individual proteins affecting specific biological processes remains a challenge. To address these hurdles, we used a network approach to aid in the selection of protein targets from synaptic proteomic data. Multiplex tandem mass tag mass spectrometry proteomic data (n = 8,311 proteins) was generated on human brain tissue from the inferior temporal gyrus (ITG) and superior frontal gyrus (SFG). Samples were obtained from the Religious Order and Rush Memory and Aging Project (ROSMAP, N = 109). These samples exhibit a range of AD pathology and are categorized into three diagnostic groups: Controls, Asymptomatic AD, and AD cases. Weighted co-expression network analysis (WGCNA) was used to construct networks of protein co-expression modules that integrate synaptic tau seed bioactivity. WGCNA identified several protein modules associated with synaptic tau seed bioactivity and phosphorylated tau levels. Module 22 was most strongly associated with synaptic tau seed bioactivity and gene ontology analysis revealed that proteins in this module were critical for RNA processing, including EIF3 complex proteins. Individual protein correlation analysis identified proteins linked to synaptic tau seed bioactivity, including SQSTM1, RPH3A, and NRN1, highlighting potential synaptic targets for experimental validation. This synaptic proteome network analysis could indicate key pathways involved in tau seed propagation and help identify human proteins that are critical for synaptic biology and synapse loss in AD.

Disclosures: E. Hobby: None. **D.A. Bennett:** None. **N.T. Seyfried:** None. **J.H. Herskowitz:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.20/V19

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

Support: Pioneer Science
National Institute for Translational Neuroscience (INNT)
CNPq
FAPERJ

Title: β-amyloid oligomers alter the temporal dynamics of CCR5 induced by learning in the hippocampus in an animal model of Alzheimer's disease

Authors: *A. TOSTA[1], K. MELLO[1], L. HEIMFARTH[2], F. CAMPOS RIBEIRO[1], S. T. FERREIRA[2], M. V. LOURENCO[1];
[1]Inst. of Med. Biochem. Leopoldo de Meis, [2]Carlos Chagas Filho Biophysics Inst., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil

Abstract: Background: The chemokine receptor CC type 5 (CCR5), known as the HIV co-receptor and for its role in the immune response, is highly expressed in the CA1 region of the hippocampus, an area essential for memory acquisition and consolidation. Increased CCL5/CCR5 signaling is associated with aging and reduced memory binding, shortening the time window for linking new memories. Although CCR5 dysregulation has been reported in Alzheimer's disease (AD), its role in memory-related processes is still poorly understood. **Objective:** We sought to investigate the expression of CCR5 and its ligand CCL5 in the hippocampus after intracerebroventricular (ICV) administration of AβOs, as well as to explore their possible involvement in mechanisms related to memory binding in the context of AD. **Methods:** In this study, Swiss mice received intracerebroventricular (i.c.v.) injections of vehicle or AβOs (100 pmol). Initially, we evaluated the gene expression of CCR5 and CCL5 in the hippocampus by RT-qPCR at 0, 8, and 24 hours after the formation of a shock-induced memory (0.65 mA). In the second set of experiments, mice were exposed to context A, received a shock (0.65 mA) 5 hours later, and were re-exposed to context A 24 hours later to assess memory retrieval. The hippocampus was collected immediately after the test to evaluate the expression of CCR5 and CCL5. Statistical analyses were performed using mixed-effects models and appropriate parametric or non-parametric tests, with significance set at $p < 0.05$, using GraphPad Prism 9. **Results:** Initial results demonstrated distinct gene expression patterns between the experimental groups. Animals injected with the vehicle showed a progressive increase in CCR5 expression over time after memory formation ($p = 0.004$), while animals treated with AβO did not show an increase in CCR5 expression ($p = 0.249$). However, no difference was observed between the experimental groups at any of the time points evaluated. We also did not observe changes in CCL5 expression. In the contextual memory association results, no differences were observed in freezing behavior between the vehicle and AβO groups. Unexpectedly, animals treated with AβO did not show an increase in CCR5 or CCL5 expression after re-exposure to context A. Instead, CCR5 levels showed a decreasing trend in animals treated with AβO ($p = 0.0592$). **Conclusions:** These results demonstrate that Aβ oligomers impair the temporal dynamics of CCR5 in response to aversive learning stimuli in mice. These results may provide a framework for understanding memory linkage dysfunction in Alzheimer's disease.

Disclosures: A. Tosta: None. **K. Mello:** None. **L. Heimfarth:** None. **F. Campos Ribeiro:** None. **S.T. Ferreira:** None. **M.V. Lourenco:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR050.21/V20

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

Title: Investigating aging and sex differences in mechanisms of memory and synaptic plasticity in an Alzheimer's disease mouse model

Authors: *S. N. OFFOR[1], L. A. SCHRADER[2], M. N. N. GHAFFARZADEHGAN[3];
[1]Cell and Mol. Biology, Tulane Univ., [2]Cell & Mol. Biol, [3]Cell and Mol. Biol., Tulane Univ., New Orleans, LA

Abstract: Investigating aging and sex differences in mechanisms of memory and synaptic plasticity in an Alzheimer's disease mouse model Sandra Offor [1], Mohammadyashar Ghaffarzadehgan [1], Jeremy Stratmann [1], and Laura Schrader [1, 21] Department of Cell and Molecular Biology and [2] Brain Institute, Tulane University, New Orleans, LA 70118Alzheimer's disease (AD) is characterized by progressive cognitive decline associated with amyloid-β (Aβ) plaque deposition, tau pathology, and synaptic dysfunction. Emerging evidence indicates significant sex differences in AD incidence, pathology, and therapeutic response, yet the synaptic mechanisms underlying these differences remain unclear. This study investigated sex-specific alterations in hippocampal synaptic plasticity and memory in the App^{NLGF} (NLGF) knock-in mouse model of AD, which develops progressive amyloidosis without artifacts associated with APP overexpression.Extracellular field recordings in hippocampus slices were used to assess long-term potentiation (LTP) at the CA3-CA1 synapse following theta-burst stimulation in young (5-6 months old) and aged (12-14 months old) mice. Young NLGF mice (n = 14 mice, 14 slices) exhibited reduced LTP magnitude compared to wild-type controls (n = 9 mice, 9 slices), ($p = 0.039$), despite no significant differences in basal synaptic transmission ($p = 0.69$). In contrast, preliminary data show that aged NLGF mice (n = 12 mice, 12 slices) did not show overall LTP deficits compared to WT mice (n = 5 mice, 5 slices, $p = 0.35$); however, sex-specific differences were emerging. Given the role of the NMDA receptor subunit GluN2B in synaptic plasticity, the selective antagonist Ro 25-6981 (5 μM) was used to determine GluN2B dependence of synaptic plasticity. GluN2B blockade reduced LTP in young mice of both genotypes (n = 30 mice, 30 slices), indicating GluN2B-dependent plasticity at early stages. Interestingly, in the aged NLGF mice, LTP remained GluN2B-dependent in males but not in females (n = 7 mice, 7 slices), revealing a sex-divergent shift in plasticity mechanisms with age. In addition, spatial memory was evaluated using the object location and object recognition memory tasks. No significant group differences were observed at 30-minute and 24-hour delays in young (n =36 mice) and aged mice (n = 27 mice). Together, these findings show age- and sex-dependent alterations in the mechanisms of synaptic plasticity in the NLGF model, with different reliance on GluN2B.

Disclosures: S.N. Offor: None. **L.A. Schrader:** None. **M.N.N. Ghaffarzadehgan:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

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Program #/Poster #: PSTR050.22/V21

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

Support: NIH Grant R15DA049260
Brigham Young University

Title: Chronic Semaglutide Partially Rescues Spatial Memory and Hippocampal Synaptic Plasticity in the Alzheimer's Disease 3xTg-AD Mouse Model

Authors: *A. TERRY[1], J. EDWARDS[1], J. NOLTE[2], B. VALENTINE[2], M. LYMAN[2], A. NELSON[2], C. MASTNY[2];
[1]Cell Biol. and Physiol., [2]Brigham Young Univ., Provo, UT

Abstract: Alzheimer's disease (AD) is characterized by progressive cognitive decline, synaptic dysfunction, and metabolic impairment. Glucagon-like peptide-1 receptor (GLP-1R) agonists, such as semaglutide, have emerged as promising neuroprotective agents due to their ability to modulate central neurometabolic pathways. However, the effects of chronic semaglutide treatment on synaptic plasticity and cognitive behaviors in AD models remain unclear. This study investigates chronic semaglutide administration on spatial memory, recognition memory, and hippocampal long-term potentiation (LTP) in triple-transgenic (3xTg-AD) mice, using wild-type (WT) mice as controls. Starting at 3 months of age, 3xTg mice received subcutaneous semaglutide injections (0.2 mg/kg) or vehicle control three times weekly. Cognitive performance was evaluated at 6-8 months using Novel Object Recognition (NOR) and Barnes maze assays. After behavioral analysis, acute hippocampal slices were prepared for extracellular field recordings to evaluate theta-burst stimulation (TBS) induced LTP at the Schaffer collateral-CA1 synapses. Analysis of fEPSP slopes 30-35 minutes post-TBS revealed significant LTP rescue in semaglutide-treated 3xTg mice compared to vehicle ($p=0.027$; n=40 slices/21 mice treated vs. 33/19 vehicle). Notably, this rescue was driven by robust, sex-specific improvement in females ($p=0.0009$; n=24/14 treated vs. 17/11 vehicle); male synaptic plasticity was unaffected ($p=0.95$; n=16/8 treated vs. 15/7 vehicle). The NOR discrimination index revealed no overall significant treatment effects ($p=0.94$; n=11 treated vs. 11 vehicle), nor with male ($p=0.81$; n=3 vs. 9) or female ($p=0.74$; n=8 vs. 2) cohorts. Ongoing evaluation continues to quantify Barnes maze spatial metrics (primary latency, errors, distance, search strategy, target quadrant occupancy) to determine cognitive outcomes. Ultimately, semaglutide shows promise for modulating hippocampal synaptic plasticity in a sex-dependent manner, highlighting its therapeutic potential in improving AD pathology.

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Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

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Program #/Poster #: PSTR050.23/V22

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

Support: Larry L. Hillblom Foundation Fellowship 2021-A-012-FEL

Title: Delivery of astrocyte secreted Chrdl1 to target synapse loss in Alzheimer's disease

Authors: *A. DEREVYANKO, A. LEE, S. YIP, Q. ASBELL, S. ROBINSON, G. PULIATTI, N. J. ALLEN;
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Abstract: Synaptic dysfunction underlies cognitive impairments observed in neurodegenerative disorders including Alzheimer's disease (AD). These deficits are driven in part by the loss of synaptic GluA2 AMPA glutamate receptors subunits, which are calcium impermeable and present at mature, stable synapses. Thus, preserving synaptic GluA2 represents a potential strategy to counteract synaptic dysfunction and cognitive decline in AD. Astrocytes are glial cells that play a central role in regulating synapse formation and stability through the secretion of synaptogenic factors. Our group identified chordin-like 1 (Chrdl1) as a protein secreted by astrocytes that specifically promotes synaptic recruitment of GluA2-containing AMPARs and the formation of stable synapses in the brain.

To investigate whether Chrdl1 can protect against the synaptic and cellular alterations associated with AD pathogenesis, I developed an AAV-based strategy to selectively overexpress Chrdl1 in astrocytes of wild-type and AD mice. Using the Tau P301S (PS19) model, which recapitulates key features of disease progression including early synapse loss, I evaluated the potential of Chrdl1 to prevent or rescue disease progression by delivering it either prior to or after synaptic deficits had emerged. Synaptic analysis in the hippocampus revealed a significant reduction in GluA2-containing synapses in Tau mice, which was restored by Chrdl1 overexpression. In addition, Chrdl1 mitigated key hallmarks of neurodegeneration, including microglial reactivity and Tau pathology burden. As an antagonist of BMP signaling, a pathway implicated in adult neurogenesis, Chrdl1 overexpression also increased the number of newly generated neurons, potentially contributing to improved disease outcomes. To determine whether these molecular changes translated into functional benefits, I examined cognitive performance. Chrdl1 overexpression initiated prior to synapse loss improved cognitive performance in the Barnes maze and fear conditioning paradigms in Tau mice.

Having established the potential of Chrdl1 to modulate AD progression in mouse models, my current research focuses on evaluating its function and translational relevance in human iPSC-derived neuronal cultures and glia-enriched cortical organoid models, for which I have optimized an astrocyte-specific viral delivery strategy.

Together, these studies will define the role of Chrdl1 overexpression in mitigating synaptic dysfunction in AD and other disorders characterized by excitatory synapse loss and establish a platform for developing astrocyte-based approaches to synaptic repair across neurodegenerative diseases.

Disclosures: A. Derevyanko: None. **A. Lee:** None. **S. Yip:** None. **Q. Asbell:** None. **S. Robinson:** None. **G. Puliatti:** None. **N.J. Allen:** None.

Poster

PSTR050: Synaptic Alterations in Alzheimer's Disease

Location: WCC Halls A-C

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Program #/Poster #: PSTR050.24/V23

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

Support: NIH Grant R44AG071386

Title: Utilizing a Functional, Human-Based Central Nervous System Model for Evaluating Neurocognitive Impairment and Therapeutic Efficacy

Authors: *K. AUTAR[1], X. GUO[2], D. G. MORGAN[3], J. J. HICKMAN[2,1];
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Abstract: While human induced pluripotent stem cells (hiPSCs) and microphysiological systems (MPS) have advanced preclinical drug assessment, bridging the translational gap requires platforms that provide clinically relevant functional readouts rather than relying solely on biomarkers. This study presents a functional human-based CNS model composed of hiPSC-derived cortical neurons and astrocytes patterned over microelectrode arrays (MEAs). Integrating these cell types successfully recapitulates long-term potentiation (LTP), the primary in vitro synaptic correlate for learning and memory. This offers a quantifiable metric for synaptic plasticity and neurotransmitter imbalances, which are essential for modeling neurodegenerative disorders characterized by cognitive impairment, such as Alzheimer's disease (AD) and frontotemporal dementia. AD pathophysiology was recapitulated via exposure to amyloid-beta42 (Aβ42) plaques and tau oligomers, and by utilizing familial AD patient-derived hiPSC-cortical networks. Exogenous Aβ42 and tau exposure effectively reproduced early- and late-stage AD phenotypes, inducing functional impairment (quantified via LTP measurements) to investigate AD drug efficacy. The model's utility for precision medicine and reproducing heterogeneous clinical presentations was validated using cortical neurons from patient-derived hiPSCs harboring PSEN1, PSEN2, and ApoE4 mutations (the latter representing a genetic predisposition for developing AD). These models successfully mimicked distinct heterogenous disease pathologies and enabled investigation of differential therapeutic responses. Finally, to evaluate neuroinflammation, a key mechanism in neurocognitive disorders, hiPSC-microglia were titrated into the neuron-astrocyte co-culture to assess the impact of varying inflammation levels. Microglia were either activated with lipopolysaccharide (LPS) to simulate generalized inflammation or Aβ42 oligomers to simulate an AD-specific pro-inflammatory state. Introducing activated microglia resulted in a ratio- and concentration-dependent suppression of synaptic plasticity, effectively simulating inflammation-induced cognitive deficits. In summary, this functional, human-based CNS model reproduces the pathophysiology and inflammatory impacts of neurocognitive disorders, providing a robust preclinical diagnostic tool for drug discovery and precision medicine.

Disclosures: K. Autar: A. Employment/Salary (full or part-time):; Hesperos, inc.. **X. Guo:** None. **D.G. Morgan:** None. **J.J. Hickman:** A. Employment/Salary (full or part-time):; Hesperos, inc..

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.01/V24

Topic: D.03. Stroke

Support: NIH Grant R01NS131227 (PI: Vahdat)

Title: Cortical-brainstem-spinal cord hyperactivation in post-stroke spasticity

Authors: *D. WANG[1], M. M. GRUDNY[2], S. VAHDAT[3];
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Abstract: Post-stroke spasticity (PSS), marked by hypertonia and hyperreflexia, is a common and debilitating complication of stroke that impedes motor recovery. Despite its prevalence, how sensorimotor pathways become imbalanced in PSS remains unclear, in part because brain and spinal cord activity have rarely been examined simultaneously. The reticulospinal tract (RST), which originates in the brainstem reticular formation, becomes hyperexcitable after corticospinal injury and has been proposed as a driver of post-stroke hypertonia; however, its contribution has not been assessed together with spinal cord activity in humans. Using simultaneous brain-spinal cord fMRI, this study aimed to localize spasticity-specific activation abnormalities along the cerebrospinal axis and test whether pontomedullary reticular formation (PMRF, RST origin) hyperactivity accompanies altered spinal activation in PSS.Healthy controls (n=26) and chronic stroke patients with (n=21) and without (n=22) spasticity performed a unilateral isometric handgrip force-control task during simultaneous brain-cervical spinal cord fMRI at 3T. Force output was normalized using percentage of maximal voluntary contraction across patients and healthy controls. Data were processed using the recently developed integrated simultaneous brain-spinal cord fMRI pipeline (FASB). Force-modulated activation was estimated in relation to applied hand force and compared across groups within a priori sensorimotor regions spanning cortex, brainstem reticular formation, and the cervical ventral horn (cluster-corrected, $Z > 2.7$, $p < 0.05$).Across all groups, the force-control task elicited the expected force-modulated sensorimotor activation along the cerebrospinal axis. Critically, relative to both non-spastic patients and healthy controls, spastic patients showed significantly greater activation in the contralesional PMRF, contralesional premotor cortex and insula, SMA, striatum, and bilateral cerebellum, as well as in the ipsilateral ventral horn ($p < 0.05$, corrected). Non-spastic patients did not differ from healthy controls in any of these regions ($p > 0.05$). These findings provide the first neuroimaging evidence linking post-stroke spasticity to PMRF and ventral cervical horn hyperactivation during volitional force production, identifying a spasticity-specific brainstem-spinal substrate of hypertonia and supporting a maladaptive role of reticulospinal output.

Disclosures: D. Wang: None. **M.M. Grudny:** None. **S. Vahdat:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

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Program #/Poster #: PSTR051.02/V25

Topic: D.03. Stroke

Support: Canadian Institutes of Health Research (CIHR)
Heart & Stroke Foundation
CIHR Project Grant
CFI and ORF Infrastructure
NSERC Discovery Grant
Pacira Biosciences Inc.

Title: Investigating the relationship of Neurophysiological Excitability Measures and Upper-Limb Spasticity Severity in Chronic Stroke

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Abstract: ***Background:*** Stroke is a leading cause of disability and is often associated with upper-limb motor impairments, including weakness and spasticity. Spasticity reflects disordered sensorimotor control and is thought to arise from altered descending motor drive and spinal reflex excitability, though its underlying neurophysiology remains poorly understood. The corticospinal tract (CST) mediates voluntary motor control and has been implicated in post-stroke motor impairment. Transcranial magnetic stimulation (TMS) and surface electromyography (EMG) offer a non-invasive avenue to assess corticospinal excitability through motor evoked potentials (MEPs). The excitability of the CST has been linked to spasticity severity indicating potential as a predictor of functional recovery post-stroke. The aim of this project was to investigate potential TMS measures and their relationship with upper-limb post-stroke spasticity severity. ***Methods:*** Chronic stroke patients with elbow and/or wrist spasticity were recruited from Parkwood Institute in London, ON. Participants' spasticity severity was assessed by summing Modified Ashworth Scale (MAS) scores across muscles, and is reported as median [IQR]. 20 stimulations were delivered using TMS over the ipsilesional first dorsal interossei (FDI) hotspot at 120% of their resting motor threshold (RMT). Average MEP amplitude and latency were calculated from EMG recordings of FDI, abductor pollicis brevis (APB), brachioradialis (BR), and pronator teres (PT) muscles. Pearson's correlations (r) were used to examine relationships between total MAS score and cortical excitability measures, including RMT, MEP amplitude and MEP latency. ***Results:*** MEPs were observed in 5 of 11 participants, whereas 6 participants showed no detectable responses. The grand mean (range) amplitude and latency of the elicited MEPs across all muscles were 275.23 (45.15-1555.35) μV and 23.43 (14.44-33.09) ms, respectively. Preliminary results in eleven people with stroke (6 female, 5 male; median age [IQR] 58 [51, 65.5] years; 7 right, 4 left hemisphere lesions; MAS 10.5 [7.75,14.5]) indicate a significant correlation between MAS scores and APB MEP latency

among participants with elicitable motor responses (MEP+) ($r(4)=0.870$, $p<0.05$). There were no other significant correlations to report. ***Discussion:*** TMS measures of excitability may be linked to clinical measures of spasticity severity. Early findings show a strong positive correlation between MAS scores and APB MEP latencies in MEP+ participants, suggesting a potential relationship between greater spasticity severity and prolonged corticospinal conduction following stroke.

Disclosures: A. Delisle: None. **S. Peters:** A. Employment/Salary (full or part-time):; Western University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pacira Biosciences Inc..

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.03/V26

Topic: D.03. Stroke

Title: Reaching assessment across nine target locations reveals spatial profiles of post-stroke upper limb impairment

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Abstract: BackgroundPost-stroke upper-limb reaching varies across the reaching workspace, whereas single-target or summary measures are limited in capturing target-location-dependent patterns of impairment and compensation.ObjectiveWe investigated whether kinematic profiles across the reaching workspace reveal systematic spatial patterns of impairment and compensation that differ by stroke severity and target location.MethodsSeventy-seven participants performed a nine-target reaching task (three heights × three horizontal positions): healthy young adults (HY, n=17), healthy older adults (HE, n=17), mild stroke impairment (FMA-UE ≥54, n=26), and moderate stroke impairment (FMA-UE <54, n=17). Kinematics were analyzed with linear mixed-effects models and Bonferroni-corrected pairwise comparisons. Muscle synergy number from surface EMG served as a supplementary measure.ResultsRelative to HY, HE showed greater shoulder abduction and trunk forward displacement (7.9 vs. 36.7 mm) with preserved movement quality. Mild stroke impairment showed greater scapular elevation at all heights (+12 to +25 mm vs. HE, all $p\leq0.041$) and greater muscle synergy number (3.33 vs. 3.91, $p=0.037$), while trunk forward displacement and movement quality remained indistinguishable from HE. Moderate stroke impairment showed greater trunk forward displacement (37 vs. 75 mm), lateral trunk displacement as an additional compensatory component (all $p<0.001$), and deterioration of movement-quality indices across all nine targets: the variability of SPARC increased fivefold (SD 0.040 vs. 0.217), and velocity peak count

increased from 3.2 to 6.0 (all $p<0.001$). Elevated targets amplified scapular elevation and trunk compensation. The high-lateral target appeared to impose the greatest demand and revealed movement-quality deficits even in mild stroke impairment.
ConclusionsWorkspace-wide reaching assessment characterizes target-location-dependent patterns of impairment and compensation after stroke, distinguishing shoulder-girdle-compensated performance in mild stroke impairment from breakdown of movement quality and trunk compensation strategy in moderate stroke impairment. The accompanying increase in muscle synergy number in mild stroke impairment warrants longitudinal investigation. These findings support multi-target reaching evaluation for detecting compensated impairment and severity-dependent transitions in motor control strategy. This approach may complement conventional impairment scales by exposing task-location-specific compensations that remain hidden in global scores.

Disclosures: H. Uchisawa: None. **K. Ikuno:** None. **Y. Igawa:** None. **K. Shomoto:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.04/V27

Topic: D.03. Stroke

Support: NIH Grant R01NS131227 (PI: Vahdat)

Title: Biomechanical and Electrophysiological Biomarkers of Upper Limb Spasticity Post-stroke

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Abstract: Spasticity is a common and disabling consequence of stroke, marked by a velocity-dependent increase in resistance to passive muscle stretch that impairs limb function and complicates rehabilitation. The clinical standard for grading spasticity is the Modified Ashworth Scale (MAS), but its examiner-dependent nature limits its reliability and sensitivity to change, leaving a need for objective reflex biomarkers that capture the biomechanical and neurophysiological components of spastic muscle behavior. Here, we aim to characterize the joint torque, surface electromyography (EMG), and Hoffmann reflex (H-reflex) responses evoked by passive wrist stretch in stroke patients and healthy controls to identify biomechanical and electrophysiological reflex biomarkers that distinguish spastic from nonspastic and control groups.Passive wrist flexion and extension stretches were applied through an approximately 90° range of motion across varying angular velocities using a Biodex dynamometer. Joint torque and surface EMG from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) were recorded simultaneously during the passive stretch. H-reflexes were elicited to assess spinal reflex excitability. Participants included healthy controls and stroke patients sorted into spastic

and nonspastic groups, based on individual results from the MAS, the Fugl-Meyer Upper Extremity assessment (FMA-UE), and the Nottingham Sensory Assessment (NSA). Torque and EMG data were processed and analyzed using a custom MATLAB pipeline.Our biomarkers for passive stretch torque and stretch-evoked EMG activity differed significantly across the spastic, nonspastic, and control groups ($p < 0.05$), with the spastic group showing elevated reflex responses. H-reflex measures of spinal reflex excitability also differed across groups ($p < 0.05$) consistent with altered excitability in spasticity. Within the spastic group, several reflex biomarkers correlated with clinical severity as graded by the MAS.Using our biomarkers extracted from torque and EMG responses to controlled passive wrist stretch, along with H-reflex measures of spinal reflex excitability, we captured distinct differences in spastic muscle behavior between the three groups. These biomechanical and electrophysiological reflex biomarkers distinguish spastic patients from nonspastic and control groups and may serve as objective complements to examiner-based clinical scoring of spasticity after stroke. Future work can apply this approach to larger cohorts and relate these measures to functional sensorimotor outcomes.

Disclosures: D. Fellhauer: A. Employment/Salary (full or part-time):; Bioengineering Department, University of California, Riverside. **N. Garro:** None. **V. Marchand-Pauvert:** None. **S. Vahdat:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.05/V28

Topic: F.04. Voluntary Movements

Title: Assessment of Movement Quality for Upper Limb Rehabilitation using Machine Learning

Authors: *S.-J. KIM[1,2], J. SUM[3,2];
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Abstract: Assessment of Movement Quality for Upper Limb Rehabilitation using Machine Learning: A Feasibility Study of LSTM and Transformer Architectures
Authors:*S.J. Kim[1], J.R. Sum[1] [1]Biomedical Engineering, California Baptist University, Riverside, CA 92504, USA
Disclosures:S.J. Kim: None, **J.R. Sum**: None
Abstracts: Evaluating upper-limb movement quality is essential for clinicians treating neurorehabilitation patients, yet existing methods are often subjective and resource-intensive. This study investigated the feasibility for a low-cost, automated, and objective system to evaluate upper-limb motion using a webcam and sequenced-based deep learning algorithms. 34 healthy subjects (25 male, 9 female) performed circular and linear tracing tasks using a custom four-link robotic device. Trial data from participants were collected separately for training and testing the

deep learning models. The device applied controlled random torque perturbations to simulate impaired motor control, while an overhead webcam extracted 2D trajectories of the shoulder, elbow, and wrist using two-dimensional (2D) marker-less human pose estimation software based on 2D MediaPipe Blazepose framework. Long Short-term Memory (LSTM) and Transformer encoder models were trained using two output formulations: 1) binary classification of movement quality (ideal vs. perturbed) and 2) continuous regression predicting spatial trajectory deviation. Both types of models successfully distinguished between ideal and perturbed trials, producing graded predictions corresponding to perturbation level (moderate vs. strong). For circular trials, the Transformer achieved superior discrimination (AUC = 0.89) compared to the LSTM (AUC = 0.83), showcasing its ability to capture long-range temporal dependencies. In contrast, the LSTM outperformed the Transformer in binary classification of the line-tracing trials (AUC = 0.93 vs. 0.76). In conclusion, consumer-grade video hardware coupled with sequence-based deep learning enables a low-cost, objective and scalable method of assessing upper-limb motor performance. While model selection is dependent on tracing task geometry, both models demonstrate strong potential for translating quantitative movement assessment from laboratory settings to scalable, home-based rehabilitation environments.

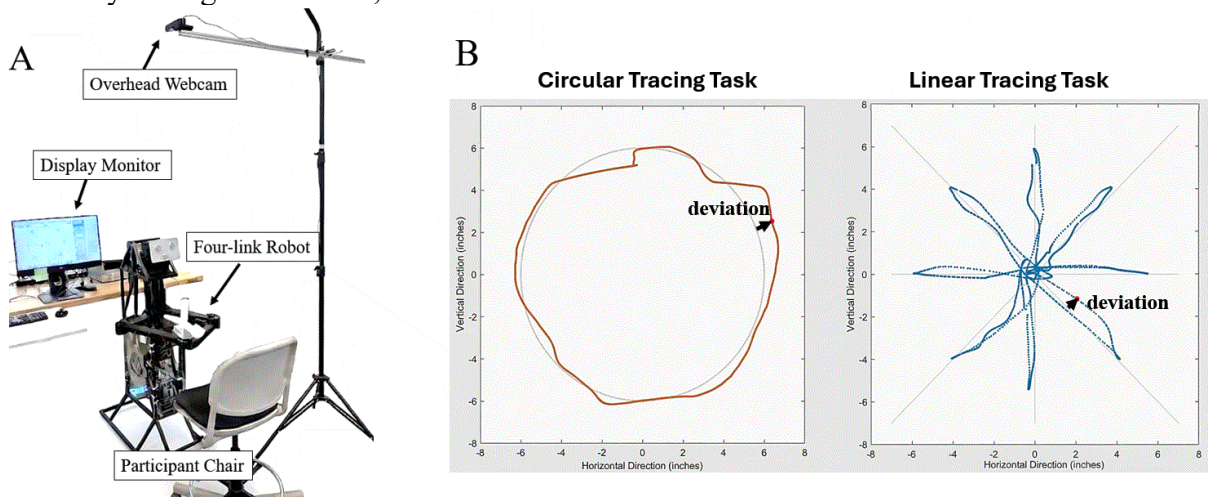


Figure. (A) Experimental setup (B) Examples of handle trajectory (circular and linear tracing tasks) relative to the ideal path.

Disclosures: S. Kim: None. **J. Sum:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

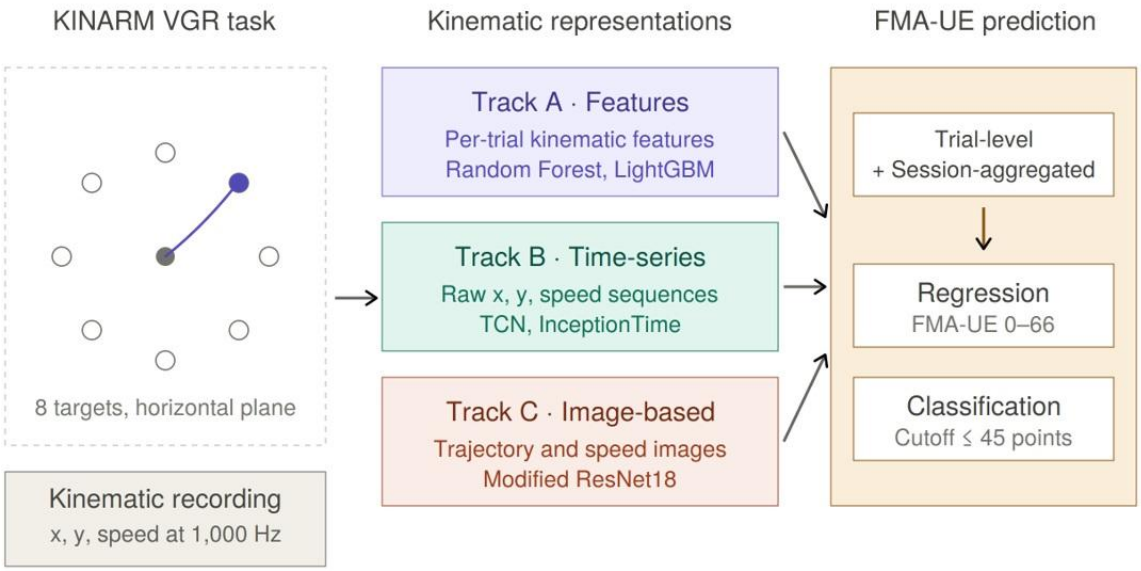
Program #/Poster #: PSTR051.06/W1

Topic: D.03. Stroke

Title: Predicting upper limb impairment in stroke survivors from a single robotic reaching movement using machine learning

Authors: *S. LEE[1], S. P. DUKELOW[2];
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Abstract: Background The Fugl-Meyer Assessment of the Upper Extremity (FMA-UE) is the gold standard for evaluating post-stroke motor impairment, but it is time-consuming and prone to variability. While robotic systems like KINARM provide objective kinematic data, interpreting high-dimensional data hinders routine clinical use. This study aims to predict FMA-UE scores using machine learning (ML) based on a single robotic reaching task and compare data representation strategies. **Methods** We retrospectively analyzed 13,414 single-trial reaching movements from 200 sessions involving 93 stroke survivors. Three distinct data representation tracks were evaluated: Track A: Handcrafted kinematic features (e.g., movement time, smoothness) using Random Forest and LightGBM; Track B: Raw time-series signals using Deep Learning models (TCN, InceptionTime); Track C: Image-based representations of trajectories and velocity profiles using ResNet. Models were evaluated at both single-trial and session-aggregated levels (averaging predictions across 80 trials). **Results** For FMA-UE score regression, the session-aggregated LightGBM model (Track A) demonstrated the highest accuracy (R^2 = 0.653, MAE = 9.02). Even at the single-trial level, Random Forest achieved predictive power (R^2 = 0.404). For binary severity classification (FMA-UE threshold of 45), the image-based ResNet-B model (Track C) achieved an outstanding ROC-AUC of 0.951 at the session level. Key kinematic predictors included movement time, number of velocity peaks, and spectral arc length (SPARC). **Conclusions** Machine learning models trained on robotic reaching data can accurately predict upper limb impairment levels in stroke survivors. While session-level aggregation provides superior precision, even a single reaching movement offers rapid screening of motor severity. Integrating ML with robotic assessments can streamline clinical workflows by providing objective, automated, and time-efficient alternatives to traditional manual assessments.



Disclosures: S. Lee: None. **S.P. Dukelow:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.07/W2

Topic: D.03. Stroke

Title: Upper limb proprioception is related to visuospatial working memory and scales with complex, sequenced movements in chronic stroke

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Abstract: Everyday tasks like preparing food and driving require the completion of complex, sequenced movements of the upper limb. This requires intact working memory to encode, store, and retrieve relevant information; proprioception to monitor and correct movements; and motor function to execute motor commands. Impairments in working memory, proprioception and motor function are common after stroke, but few studies have assessed how they interact to produce complex movements. Here, we aimed to examine how impaired proprioception after stroke affects proprioceptive working memory for reproducing complex, sequenced movements. We hypothesized that the inability to commit proprioceptive-based information to working memory significantly impacts complex, sequenced movement execution. Individuals with stroke (N=30) and age-matched controls (N=21) completed a complex, sequenced movement task (HEART). Here, a robot passively moved the more affected limb in individuals with stroke (randomized in controls), through a sequence of 1-5 targets without vision. Participants were told to remember the sequence and actively reproduce it with the same limb. They also completed robotic assessments of motor (Visually Guided Reaching (VGR)), proprioceptive (Kinesthetic Matching (KIN)), and visuospatial working memory (Paired-Associates Learning (PAL)) function. HEART was quantified using Dynamic Time Warping (DTW), with lower values indicating better matching performance. VGR, KIN and PAL were quantified using Task Scores, with scores >1.96 being significantly different from controls. We found that 10/30 stroke participants had impaired proprioception and significantly worse HEART scores (DTW=391) compared to stroke participants without proprioceptive impairments (DTW=160, $p=0.01$) and controls (DTW=119, $p<0.01$). As sequence length increased, HEART was significantly worse for stroke participants with proprioceptive impairments ($\beta_1=97$) compared to those without ($\beta_1=65$, $p=0.03$) and controls ($\beta_1=59$, $p=0.01$). Regardless of impairment, PAL was significantly related to HEART for all individuals with stroke ($\rho=0.69$, $p<0.01$). Further, we found that PAL was significantly related to KIN ($\rho=0.43$, $p<0.01$), but not VGR ($\rho=0.21$, $p=0.14$) for all participants. These results suggest that a proprioceptively-based task that taxes working memory reveals sensorimotor impairments of the upper limb. This suggests that impaired proprioception after stroke significantly affects the ability to perceive and reproduce complex, sequenced movements, and as sensory-cognitive load increases, errors increase for stroke participants with proprioceptive impairments.

Disclosures: A. Decarie: None. **J.E. Hoh:** None. **T. Singh:** None. **J.A. Semrau:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.08/W3

Topic: D.03. Stroke

Support: NIH NINDS R01NS130210

Title: Quantifying impairment of finger coordination in 3D during precision grip after stroke

Authors: *C. BYRD[1], D. RAI[1], T. MA[2], J. D. BROWN[3], J. XU[1];
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Abstract: Recovery of upper limb function after stroke is often incomplete; 40-80% of survivors do not regain full upper extremity function by 3 to 6 months post-stroke (Dobkin & Carmichael, 2016). Even when gross arm movement returns, deficits in coordinated multi-digit manipulation frequently persist, limiting precision grip performance in daily activities (Bleyenheuft & Gordon, 2014). Prior work has established that stroke impairs grip force scaling and anticipatory digit control (Nowak et al., 2003; Bleyenheuft & Gordon, 2014); however, whether these deficits extend to the spatiotemporal coordination of multi-finger precision grip remains unclear. Here, we quantified three-dimensional (3D) spatiotemporal coordination during precision grip in stroke survivors, comparing paretic and non-paretic hands.
Ischemic stroke survivors (n=6; 63±11 yrs, range 2.2-43 mo post-stroke, 1F/5M) performed thumb-to-finger opposition grip tasks (Thumb-Index and Thumb-Ring) in a 3D virtual environment using a custom multi-digit isometric force measurement device (Hand Articulation Neurotraining Device; HAND) with real-time visual feedback of fingertip position. Outcome measures included spatial (grip angle) and temporal (touch timing and trajectory synchronization) variables, analyzed across active-active, active-passive, and passive-passive finger pairs where applicable. Linear mixed-effects models were fit for each outcome variable. We predicted coordination deficits in the paretic hand compared to the non-paretic hand.
The paretic hand showed a significantly greater inter-digit touch interval compared to the non-paretic hand ($p=0.004$). Active-active trajectory synchronization was significantly reduced in the paretic hand ($p=0.018$). Grip angle, active-passive and passive-passive trajectory synchronization did not differ significantly by hand. The results provide preliminary evidence that post-stroke precision grip impairment is more pronounced in temporal coordination, implying that spatiotemporal finger metrics may reveal coordination deficits of the paretic hand after stroke.

Disclosures: C. Byrd: None. **D. Rai:** None. **T. Ma:** None. **J.D. Brown:** None. **J. Xu:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.09/W4

Topic: F.04. Voluntary Movements

Support: VA Rehabilitation Research and Development Service Grant I01 RX003511

Title: The effects of TMS across non-primary motor areas paired with practice on reaching behavior and cortical connectivity after stroke

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Abstract: Each stroke survivor has unique structural damage and preserved network integrity, yet lesions in the depths of the frontal lobe often lead to hemiparesis. Upper-limb function rarely recovers fully after rehabilitation. Non-primary motor regions, such as dorsal/ventral premotor cortex (PMd/PMv) and posterior parietal cortex (PPC), shape reach planning and execution and may support post-stroke recovery. Here, we test how perturbing these regions affects reaching, whether connectivity explains performance variability, and how stimulation paired with practice influences motor performance and network connectivity. A total of 19 individuals with chronic internal capsule stroke and 25 intact adults completed a planar reaching task using KINARM with time-locked transcranial magnetic stimulation (TMS) applied to bilateral PMd, PMv, PPC, and a control site. A 10-Hz triple-pulse TMS train was delivered in the planning phase. Straightness and smoothness were calculated relative to the control site. Functional connectivity among the target sites was compared between groups and associated with behavioral changes. A subset of 10 stroke participants completed a practice-paired contralesional PPC TMS protocol. Reaching performance was assessed pre/post stimulation with functional near-infrared spectroscopy (fNIRS) recorded during the Box and Blocks task to measure cortical activity and connectivity. We found significant resting-state connectivity differences among PPC and premotor regions across groups. TMS effects varied by movement direction. For forward movements, contralesional PMd/PPC stimulation resulted in straighter and smoother trajectories, and ipsilesional PPC/PMd stimulation led to lower deviations. For movements towards the trunk, reaching was mostly unchanged, with limited reductions in straightness and smoothness after contralesional PMd or ipsilesional PPC stimulation. Repeated practice improved smoothness whereas the effect of contralesional PPC stimulation was evident in greater contralesional premotor activation, increased contralesional connectivity, and reduced ipsilesional connectivity. In conclusion, premotor-parietal network changes may contribute to stimulation response variability. TMS effects depended on task demands, with forward movements, which are more impaired in stroke, being more sensitive. Stimulation paired with practice influenced cortical activity and connectivity while behavioral changes appeared largely practice-related, thus far. Future work will optimize stimulation targets and protocols toward personalized and effective therapy for upper-limb impairments after stroke.

Disclosures: G. Haddadshargh: None. **R. de Freitas:** None. **F. Liu:** None. **A. Boos:** None. **J. Mak:** None. **X. Fang:** None. **G.F. Wittenberg:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.10/W5

Topic: F.04. Voluntary Movements

Support: JSPS Research Fellowships for Young Scientists DC1 (26KJ1685)

Title: Bilateral proprioceptive-motor coupling induces muscle activity in a passively moved hand via the contralateral corticospinal pathway

Authors: *Y. SATO[1,2,3], Y. TANG[1,2,3], H. NAKANO[2,4], J. PARK[2,5], T. MORITA[1,2], E. NAITO[1,2];
[1]Grad. Sch. of Frontier Biosciences, The Univ. of Osaka, Suita, Japan; [2]Ctr. for Information and Neural Networks, Advanced ICT Res. Institute, Natl. Inst. of Information and Communications Technol., Suita, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan; [4]Grad. Sch. of Hlth. Sci., Kyoto Tachibana Univ., Kyoto, Japan; [5]Symbiotic Intelligent Systems Res. Center, Inst. for Open and Transdisciplinary Res. Ini, The Univ. of Osaka, Suita, Japan

Abstract: To restore paretic finger motor functions in patients with severe stroke, passive movement has been traditionally used in rehabilitation, but this doesn't always induce muscle activity. In this study, we propose bilateral proprioceptive-motor coupling (BPMC) approach and test hypothesis that passive movement of one hand synchronized with active movement of the opposite hand induces muscle activity on the passive side.This study aimed to reveal the effectiveness of the BPMC approach and to elucidate its underlying neural mechanisms in healthy young adults.In experiment 1, we evaluated changes in muscle activity of extensor digitorum communis on passive side measuring EMG. Participants wore leader/follower-type exoskeleton robots on both hands. They repeated In-phase task (IN), where the robot passively extended the right fingers in sync with the active left finger extension. As control conditions, they also performed bilateral passive task (BP) where both fingers were passively extended simultaneously and out-of-phase task (OUT) where the right fingers were passively moved in antiphase to the active left finger extension. In experiment 2, we investigated brain activity using fMRI during the IN, where the experimenter manually passively extended the right index finger in sync with active left index finger extension, and during its corresponding BP and OUT. In experiment 3, we investigated the causal relationship between EMG on the passive hand and the contralateral motor cortex (M1) using transcranial magnetic stimulation (TMS). The left M1was stimulated by TMS, and the cortical silent period (CSP) was assessed during IN.EMG of the passive hand significantly increased during both the IN and OUT, but not during the BP. Only through the repetition of the IN, the amplitude of EMG gradually increased. IN significantly more activated the hand section of the left M1 when compared with the OUT. The hand section

of the right M1 enhanced their functional coupling with the left hand section during the IN as compared to the OUT. Furthermore, the right supplementary motor area enhanced functional coupling with the left hand section during the IN when compared to the BP. And TMS to the left M1 induced CSP in EMG of passively moved hand during IN.The results suggest that the BPMC approach can be an effective method to induce muscle activity in a passively moved hand, and that its underlying neural mechanisms are facilitation of functional couplings between the bilateral M1 and between the M1 and higher-order motor intention area. These neural activities result in the induction of muscle activity on the passively moved hand via the corticospinal pathway from the contralateral M1.

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Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.11/W6

Topic: F.04. Voluntary Movements

Support: P2CHD086844
R25HD106896

Title: Modulating Fronto-Parietal Cortical Networks for Improving Balance in Stroke - a theta burst TMS study

Authors: *K. K. KUKKAR[1], T. PHAM[2], D. PHAM[2], P. J. PARIKH[2];
[1]Hlth. and Human Performance, [2]Univ. of Houston, Houston, TX

Abstract: Post-stroke, adults often undergo brain reorganization affecting the cortical network connectivity, which may affect balance control and the generation of effective responses to prevent a fall when their balance is challenged. Our recent balance studies using electroencephalography (EEG) showed that stronger sensorimotor communication between the supplementary motor area and the posterior cingulate cortex is crucial for dynamic balance in a healthy system. Stroke participants, in contrast, relied on attention and monitoring-related communication between SMA and bilateral prefrontal cortices to support balance. We hypothesized that facilitating SMA-prefrontal balance-EEG connectivity using repetitive transcranial magnetic stimulation (rTMS) to SMA may support recovery in stroke participants. In this study, we investigated the effects of a single session of facilitatory theta burst stimulation (iTBS; a form of rTMS) over ipsilesional SMA on its EEG functional connectivity with PCC and bilateral prefrontal regions in chronic stroke patients. We also studied the effects of iTBS over SMA on laboratory-based balance performance using the foot center of pressure measures. Ten stroke participants received either offline iTBS over SMA or sham iTBS in two counterbalanced sessions. During each session, we investigated the cortical network dynamics using the whole-

head electroencephalography (EEG) while participants performed a challenging balance task. During the balance task, participants were instructed to maintain their balance while standing on a sway-referenced balance platform. iTBS significantly increased EEG functional connectivity from SMA to dlPFC when compared with sham stimulation, enhancing cognitive circuit activation. iTBS versus sham stimulation reduced connectivity from SMA to PCC. iTBS increased the RMS of the foot center of pressure in the anterior-posterior direction when compared with sham stimulation, suggesting a strategy that seeks to maximize maneuverability to perform the challenging balance task. The findings suggest that a single session of iTBS over SMA can increase the compensatory functional connectivity between SMA and dlPFC, which may result in improved balance outcomes in stroke participants.

Disclosures: K.K. Kukkar: None. **T. Pham:** None. **D. Pham:** None. **P.J. Parikh:** None.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.12/W7

Topic: D.03. Stroke

Support: AHA Award 25CDA1439419 (AMH)
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VA CDA 1IK2RX004237 (DJL)
Center for Neurorestoration and Neurotechnology, (N2864-C) U.S. Department of Veterans Affairs, Rehabilitation Research and Development Service, Providence, RI

Title: Shared structure between abnormal resting posture in the hemiparetic arm and resting posture in the healthy arm

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Abstract: Most strokes result in motor impairment - hemiparesis - which often manifests as abnormal arm posture at rest (e.g. flexor posture). The mechanisms behind this sign of hemiparesis remain unclear. Emerging evidence suggests that abnormal resting posture may arise from excessive activation of posture-related neural circuits that can normally contribute to healthy motor control - e.g. the contralesional corticoreticulospinal tract. This idea implies that posture abnormalities after stroke are not entirely novel, but instead exaggerated manifestations of patterns detectable in healthy individuals. If that were the case, then, examining the healthy motor system could illuminate the mechanisms of post-stroke arm posture, revealing targets for neurorehabilitation; whereas, examining post-stroke posture could illuminate the neuroscience of

how arm posture is controlled in general. Here we thus compared the resting posture dynamics of 14 stroke patients and 11 healthy controls. Participants were strapped to an arm sled and passively moved while holding the handle of a 2D planar robot. The robot slowly moved their arm and held it in different configurations, defined by specific shoulder and elbow angle combinations. Participants were instructed to relax, so that any involuntary resistive forces measured would quantify abnormality in resting posture. We calculated the elbow and shoulder torques corresponding to these resistive forces using inverse dynamics. In line with previous work, stroke patients showed marked resting posture abnormalities which were characterized by a propensity for flexion and scaled with overall motor impairment (Fugl-Meyer Upper Extremity scale, $p=0.0062$). Healthy controls showed torque/angle relationships that mirrored those in stroke, with reduced magnitude. Elbow flexor torque - a key component of flexor posture - significantly increased with elbow extension in both groups (both $p<0.001$), with a ~2-3x steeper slope in patients. Separate analyses revealed that the structure of resting posture biases in patients was strikingly similar to controls: the average across-position posture bias pattern in patients explained, on average, >60% of variability in healthy participant patterns, with an average weight of $\beta=0.5$. These findings indicate that resting posture patterns in healthy individuals are scaled-down versions of resting posture abnormalities observed in stroke, in line with a shared neural substrate that is abnormally overactive in stroke. Examining healthy arm posture may thus provide insights into the neural mechanisms behind abnormal posture in stroke, identifying potential targets for neurorehabilitation.

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Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.13/W8

Topic: D.03. Stroke

Support: IITP 2021-0-00742
KHIDI RS-2023-0026
NFR RS-2026-1013

Title: Deep Back Muscle Cross-Sectional Area in Chronic Stroke: Inter-Rater Reliability, Longitudinal Stability, and Association with Balance Function

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Abstract: Trunk muscle dysfunction contributes to postural impairment after stroke, yet longitudinal morphological data on deep back muscles in chronic stroke survivors remain scarce. This study aimed to (1) evaluate the inter-rater reliability of CT-based deep back muscle cross-sectional area (CSA) measurement, (2) characterize longitudinal CSA changes over 24 months, and (3) examine the association between CSA and functional balance in individuals with chronic stroke. Thirty adults with chronic stroke (22 men, 8 women; age 61.8 ± 11.0 years; time since stroke 28.8 ± 16.3 months) underwent CT imaging at baseline (V0), 12 months (V1), and 24 months (V2). Two independent raters measured bilateral deep back muscle CSA at each time point. Inter-rater reliability was evaluated using intraclass correlation coefficients (ICC, absolute agreement). Longitudinal changes in mean bilateral CSA were assessed using a linear mixed-effects model with subject-level random intercepts to accommodate repeated measures and variable follow-up availability. Functional assessments included the Berg Balance Scale (BBS), Trunk Impairment Scale (TIS), Functional Ambulation Category (FAC), Timed Up and Go (TUG), and National Institutes of Health Stroke Scale (NIHSS). Spearman correlation analysis examined associations between baseline mean bilateral CSA and functional measures. Inter-rater reliability was good to excellent across all time points and sides (ICC range: 0.765-0.914). Longitudinal analysis revealed no statistically significant change in mean bilateral CSA over 24 months (V1 vs V0: $\beta = +40.6$ mm², $p = 0.123$; V2 vs V0: $\beta = -61.6$ mm², $p = 0.082$), indicating relative morphological stability over time. No significant affected-to-unaffected side asymmetry was observed at any time point (all $p > 0.05$). Baseline mean bilateral CSA showed a moderate positive correlation with BBS score ($\rho = 0.442$, $p = 0.024$, $n = 26$ with available BBS data). Correlations with TIS, FAC, TUG, and NIHSS were not statistically significant. CT-based deep back muscle CSA measurement demonstrated good to excellent inter-rater reliability in chronic stroke survivors and may serve as a reproducible quantitative imaging biomarker. No progressive decline or affected-side asymmetry was detected over 24 months, suggesting relative stability of deep back muscle morphology during the chronic phase of stroke. The observed association between CSA and balance function suggests that deep back muscle morphology may be relevant to postural performance, warranting further investigation.

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Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

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Program #/Poster #: PSTR051.14/W9

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI Grant-in-Aid for Research Activity Start-up JP24K23061

Title: Target-speed-dependent post-movement beta synchronization during a VR-based lower-limb timing task

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Abstract: Post-movement beta synchronization (PMBS) is considered to reflect sensorimotor processing related to movement evaluation and termination and has been shown to increase with movement speed in healthy individuals. However, it remains unclear whether such modulation is preserved during lower-limb timing tasks or altered after stroke. This study investigated PMBS during a virtual reality (VR)-based lower-limb timing task in healthy young adults and patients with stroke. Eight healthy young adults (24.9 ± 2.6 years, range: 21-30 years; 3 females) and two male patients with chronic stroke (aged 49 and 52 years) participated in a first-person VR task. While seated, participants raised their thighs to intercept a virtual object approaching at a predefined timing. Two target-speed conditions were used: fast (14 m/s) and slow (11 m/s). EEG was recorded from 15 channels, and beta-band activity was analyzed using wavelet-based time-frequency analysis. PMBS was defined as the mean beta power change within a 200-ms window centered on the post-movement beta rebound peak. The patients additionally performed the VR task for 20 min/day over two weeks alongside their prescribed rehabilitation program and were reassessed after training. PMBS was observed in healthy participants under both target-speed conditions. Mean PMBS tended to be greater in the fast condition than in the slow condition (slow: 18.38 ± 20.43%, fast: 28.58 ± 28.31%), consistent with previous reports. Both patients successfully performed the VR task, and task performance improved in one patient following training. Longitudinal analysis in the patient with complete EEG data showed increased PMBS after training, particularly in the slow condition. These preliminary findings demonstrate that PMBS can be quantified during a VR-based lower-limb timing task and is modulated by target speed. The increase in PMBS observed after training may reflect partial restoration of post-movement cortical processing, including sensory feedback evaluation and re-stabilization of sensorimotor networks. PMBS may therefore provide a useful neurophysiological marker of sensorimotor recovery after stroke.

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Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

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Topic: D.03. Stroke

Support: NIH R01 1R01NS144556-01A1
JAX Startup Funds

Title: Circuit plasticity underlying bimanual motor control after stroke

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Abstract: Bimanual motor function is impaired after cortical stroke, yet few studies have assessed post-stroke bimanual dexterity. This leaves a significant knowledge gap in how deficits evolve longitudinally after stroke and mechanisms that can be therapeutically targeted. Using a bimanual string-pulling task, we developed a deep-learning based quantitative framework to measure post-stroke deficits. Trained C57BL6/J mice were induced with a photothrombotic stroke to the primary motor cortex (MOp). Pose estimation and behavioral classification models quantified high-speed motor performance. Post-stroke deficits in speed, bilateral paw synchrony, grasp, and emergence of compensatory movements were detected throughout testing (8 weeks). We find that while bimanual deficits persist, some function recovers spontaneously via endogenous plasticity. The secondary motor cortex (MOs) is necessary for coordination of fine motor tasks. Increased plasticity in MOs is associated with improved post-stroke outcomes and may act as a substrate for endogenous repair. To identify circuits causal of bimanual motor control and spontaneous recovery, we used cell-type specific optogenetics to probe sub-classes of intratelencephalic (IT) neurons in the MOs including those projecting contralaterally to the striatum (MOs cs-IT) or to the contralateral cortex (MOs cc-IT). For circuit specific dissections, MOp, MOs cc-IT, or cs-IT were silenced mid-lift using a custom built closed-loop optogenetic system. Silencing MOp mid-lift resulted in immediate lift inhibition, reversed after perturbation, showing MOp dynamics are critical for string pulling. Similar effects were observed with MOs silencing. IT tract perturbations mirror MOs; however, cc-IT silencing resulted in longer re-initiation latencies, showing deficits that surpass the perturbation period. Post-stroke, perturbation effects were more robust with a significantly longer delay to re-initiate a subsequent pull across all animal cohorts, with cs-IT additionally displaying evoked maladaptive actions not seen pre-stroke. However, as stroke progresses from acute to chronic, impairment reduced in magnitude in cs-IT animals but increased in cc-IT animals, suggesting sub-class specific roles in endogenous recovery. In summary, the establishment of a bimanual motor test to quantify stroke deficit allows circuit specific dissection of post-stroke repair mechanisms. We show that bimanual dexterity is significantly impaired longitudinally and that IT neurons serve as substrate for endogenous plasticity post-stroke with projection-specific differences in necessity for task completion after stroke.

Disclosures: K. Martin: A. Employment/Salary (full or part-time):; The Jackson Laboratory, Tufts University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NINDS, JAX Startup Funds. **M. Alasoadura:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NINDS, JAX Startup Funds. **M. Joy:** A. Employment/Salary (full or part-time):; The Jackson Laboratory. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NINDS, JAX Startup Funds. Other; Tufts University.

Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR051.16/W11

Topic: D.03. Stroke

Support: NIH Grant R01NS131227 (PI: Vahdat)

Title: Longitudinal characterization of Hyperreflexia and Hypertonia following stroke in mice

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Abstract: Post-stroke spasticity (PSS) is a debilitating complication of cerebrovascular accidents, characterized by hypertonia and hyperreflexia, that significantly impairs motor recovery in stroke survivors. Despite its clinical prevalence, the neurophysiological mechanisms underlying PSS remain poorly understood, partly due to the lack of validated animal models that recapitulate the full spasticity phenotype. Here, we validate a robust mouse model of PSS and introduce a novel method for measuring hypertonia in vivo. Male C57BL/6J mice (n=14) underwent photothrombotic stroke targeting the sensorimotor cortex and striatum; sham-operated mice (n=9) served as controls. H-reflexes were recorded from the flexor carpi radialis (FCR) muscle of the contralateral forelimb via median nerve stimulation at low and high frequencies. Rate-dependent depression (RDD) was assessed by comparing peak-to-peak H-reflex amplitudes between stimulation conditions at baseline and at 4, 15, 22, and 31 days post-stroke. To quantify hypertonia, the contralateral forepaw was firmly secured to a high-precision force transducer and subjected to passive wrist flexion-extension movements at low and high velocities. Velocity-dependent increases in resistive force and the wrist-angle threshold for evoking stretch reflexes were compared across time points and groups. Behavioral assessments, including Catwalk gait analysis and the rotating beam test, were performed one day prior to each electrophysiological and biomechanical session to characterize functional motor deficits.RDD was significantly reduced across all post-stroke time points ($p < 0.05$), with the greatest attenuation observed at D22 ($p < 0.01$), indicative of progressive hyperreflexia. Velocity-dependent resistive force was reduced and stretch reflex threshold was elevated early after stroke (D3), indicating decreased muscle tone. In contrast, by D22, resistive force was increased and stretch reflex threshold was reduced relative to both baseline and sham animals ($p < 0.01$), consistent with the delayed emergence of hypertonia. Catwalk analysis revealed significant alterations in left forepaw print position at D3 and D30 ($p < 0.05$), as well as reduced step number at D3 and D21 post-stroke ($p < 0.05$).These findings validate a robust mouse model of PSS that recapitulates both hypertonia and hyperreflexia following photothrombotic stroke, while introducing a novel biomechanical approach for quantifying hypertonia in vivo. The convergence of spasticity indices with behavioral motor deficits strengthens the translational relevance of this model.

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Poster

PSTR051: Stroke: Changes in Cortical Activity and Motor Control

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Program #/Poster #: PSTR051.17/W12

Topic: D.03. Stroke

Support: RS-2025-25459402
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Title: Synergistic post-stroke recovery via mTOR signaling and activity modulation leads to selective enhancement of connectivity between the rostral forelimb area and peri-infarct corticospinal neurons

Authors: *H. KIM[1,6], S. JEE[2,6], J. YOON[8], H. SEO[9,6], Y. SEO[10], B. JANG[11], Y. BAE[3,6], E. LEE[1,6], B. PARK[4,7], B. G. KIM[12,6,5];
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Abstract: Ischemic stroke remains a leading cause of persistent motor disability, primarily because of disruption of established neural pathways. Here, we investigated a combinatorial strategy designed to amplify post-ischemic neuroplasticity by pairing genetic enhancement of axonal growth potential with activity-dependent rehabilitation. We conditionally deleted the phosphatase and tensin homolog (*PTEN*), a key negative regulator of intrinsic axonal growth and upstream suppressor of mTOR signaling, specifically in the rostral forelimb area (RFA), followed by targeted ischemic lesioning of the caudal forelimb area (CFA). Intracortical axonal sprouting was quantitatively assessed using neuroanatomical tracing combined with a machine learning-assisted mapping algorithm. RFA-specific PTEN deletion substantially enhanced axonal sprouting toward the peri-infarct zone through mTOR activation-dependent axonal growth mechanisms, accompanied by significant improvements in motor task performance. To further leverage activity-dependent mechanisms, we administered botulinum toxin A into the non-paretic forelimb, imposing forced use of the impaired limb and augmenting neuronal activity in motor circuits. Although rehabilitation alone was insufficient to drive meaningful axonal outgrowth, its combination with PTEN deletion produced synergistic functional gains that

exceeded those of either intervention alone. To interrogate underlying mechanisms, pseudorabies virus (PRV) retrograde tracing revealed that activity-dependent training recruited a broader population of corticospinal neurons into the reorganized motor network. High-resolution imaging further confirmed that PTEN-deficient sprouted axons formed synaptic appositions with PRV-labeled, task-relevant corticospinal neurons. Notably, RFA axons selectively innervated newly recruited peri-infarct corticospinal neurons, with enriched targeting of superficial layers. Chemogenetic inhibition using DREADDs further confirmed the causal necessity of this reorganized connectivity between RFA and peri-infarct corticospinal neurons for post-stroke motor recovery. These findings suggest that PTEN deletion establishes the anatomical substrate for repair, while rehabilitative training functionally integrates newly formed connections into task-relevant motor circuits. This dual-modality approach offers a compelling framework for developing novel neurorestorative strategies targeting stroke-induced chronic motor deficits.

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Poster

PSTR052: Stroke: Pathophysiology

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Program #/Poster #: PSTR052.01/W13

Topic: D.03. Stroke

Support: NIH R01NS048216
IK6BX005647

Title: A new Tmem119-Cre$^{ERT2+/-}$; Nhe1$^{f/f}$ conditional knockout mouse line shows reduced acute brain injury after ischemic stroke

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Abstract: In our previous study, selective deletion of microglial Slc9a1, which encodes Na^+/H^+ exchanger 1 (NHE1), in Cx3cr1-Cre$^{ER+/-}$;Nhe1$^{f/f}$ mice accelerated post-stroke neurological function recovery, promoted restorative microglial activation, and enhanced oxidative phosphorylation (OXPHOS)-associated immunometabolic reprogramming and phagocytic activity after ischemic stroke (Song et al., 2018; Song et al., 2022). However, microglial Nhe1 deletion in Cx3cr1-Cre$^{ER+/-}$;Nhe1$^{f/f}$ stroke mice did not reduce acute infarct volume after ischemic stroke (Song et al., 2018). To further investigate the role of microglial NHE1 in regulating microglial metabolism and immune cell function with an improved microglial specificity, we generated an inducible Tmem119-Cre$^{ERT2+/-}$;Nhe1$^{f/f}$ conditional knockout mouse line. Tmem119-Cre$^{ERT2+/-}$;Nhe1$^{f/f}$ knockout mice (cKO) and Tmem119-Cre$^{ERT2-/-}$;Nhe1$^{f/f}$ littermate control mice (Control) received tamoxifen for five consecutive days, and at 30-day

post injection, they were subjected to transient middle cerebral artery occlusion (tMCAO) followed by reperfusion. Cerebral blood flow (CBF) was monitored by laser speckle imaging, and infarct volume and hemispheric swelling were assessed by 2% TTC staining at 24 hours after stroke. Both control and Nhe1 cKO mice showed comparable acute CBF reduction during MCAO, indicating successful ischemic induction. At 24 hours after tMCAO, Nhe1 cKO mice displayed improved ipsilateral CBF recovery compared with control mice (89.88 ± 1.67% vs. 82.75 ± 2.15% of baseline, $p = 0.021$). Nhe1 cKO mice also exhibited significantly reduced infarct volume (55.13 ± 9.23 vs. 91.00 ± 10.46 mm^3, $p = 0.022$) and decreased hemispheric swelling (17.93 ± 1.61% vs. 24.61 ± 2.05%, $p = 0.022$). In parallel, microglial activation at 3 days post-stroke was characterized in control and cKO stroke brains to assess inflammatory profiles and potential epigenetic reprogramming after stroke. Together, these findings suggest that Cx3cr1-$Cre^{ER+/-}$;$Nhe1^{f/f}$ and Tmem119-$Cre^{ERT2+/-}$;$Nhe1^{f/f}$ knockout mice exhibit distinct changes in acute infarct volume after ischemic stroke. In addition, both models illustrate a detrimental role of microglial NHE1 activation in ischemic brain injury and brain edema. Targeting microglial NHE1 may represent a potential strategy to limit post-stroke neuroinflammatory damage.

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Poster

PSTR052: Stroke: Pathophysiology

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Topic: D.03. Stroke

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Title: Microglial TGF-β1 coordinates the multicellular post-stroke reparative process via regulating metabolic reprogramming, extracellular matrix, and immune infiltration

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Abstract: Ischemic stroke triggers complex multicellular responses that coordinate inflammation, tissue remodeling, and repair. Myeloid TGF-β signaling is known to maintain microglial homeostasis under physiological conditions, but its role in shaping post-stroke recovery remains unclear. Here we show that myeloid-derived TGF-β1 is a key regulator of the

injured brain environment in stroke. Conditional deletion of *Tgfb1* in myeloid cells did not affect the infarct area in the acute stage of stroke. Instead, it impaired functional recovery following stroke and reshaped microglial transcriptional states. scRNAseq analysis show that deletion of myeloid *Tgfb1* reestablishes microglia immature phenotype that persists in the ischemic environment. These changes were accompanied by marked alterations in lipid metabolic programs and by reduced *Trem2* expression, indicating disruption of cholesterol-handling pathways. Loss of myeloid TGF-β signaling also impaired the induction of a repair-associated microglial program after stroke, characterized by reduced expression of extracellular matrix remodeling and tissue repair genes, including *Spp1, Sparc* and *Fn1*. These changes were accompanied by altered astrocyte and fibroblast responses within the glial scar and increased accumulation of $CD8^+$ T cells in the post-ischemic brain. Depletion of $CD8^+$ T cells rescued cognitive deficits in myeloid *Tgfb1*-deficient stroke mice while motor impairments remained unchanged. Together, these findings identify myeloid TGF-β1 as a central regulator of metabolic, structural, and immune programs that shape tissue repair and functional recovery after ischemic stroke.

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Poster

PSTR052: Stroke: Pathophysiology

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Topic: D.03. Stroke

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KAKENHI 23K27330
KAKENHI 24K22166
KAKENHI 26K02326

Title: Astrocytic SPP1 contributes to neurological dysfunction after cerebral ischemia

Authors: *H. NAKAJIMA[1], N. KATO[1], H. SHIRAKAWA[2,1];
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Abstract: Cerebral ischemia leads to a wide range of neurological dysfunctions and can be life-threatening. Importantly, infarct volume does not always correlate well with functional outcomes, suggesting that neurological dysfunction cannot be fully explained by neuronal cell death alone. Astrocytes are the most abundant glial cells in the central nervous system and serve as key regulators of synaptic transmission, metabolic support, and network excitability. Astrocytes become “reactive astrocytes” after cerebral ischemia, exhibiting marked changes in gene expression and function that contribute to disease pathogenesis. Therefore, elucidating the molecular mechanisms by which reactive astrocytes contribute to pathogenesis is of considerable interest. However, most previous studies have analyzed astrocytic molecular responses in severe

ischemia models, in which secondary responses associated with extensive cell death may mask intrinsic astrocytic responses emerging at earlier stages of ischemia. To clarify these intrinsic responses independent of extensive cell death, we employed a mild cerebral ischemia model using 15-minute transient middle cerebral artery occlusion (MCAO) in mice. Although no apparent infarction was observed in this model, expression of the astrocytic reactivity marker GFAP was markedly increased. To further characterize molecular changes in astrocytes, we isolated forebrain astrocytes by fluorescence-activated cell sorting and performed bulk RNA sequencing, which identified Secreted phosphoprotein 1 (*Spp1*) as one of the most highly upregulated genes. Astrocytic *Spp1* was further upregulated in the 45-min MCAO model and showed higher expression than in other cell types. While SPP1 has been implicated in ischemic pathology, the functional contribution of astrocytic SPP1 remains unclear. We therefore generated an adeno-associated virus (AAV) vector expressing miRNA targeting *Spp1* under an astrocyte-specific promoter and evaluated its role in the 45-min MCAO model. Astrocyte-specific *Spp1* knockdown significantly improved neurological severity scores and rotarod performance, whereas infarct volume was unchanged. Moreover, whole-brain c-Fos imaging revealed that ischemia-induced reductions in neuronal activity across multiple brain regions, including the hypothalamus, were partially restored by astrocyte-specific *Spp1* knockdown. Together, these findings identify SPP1 as a highly inducible astrocytic molecule and suggest that astrocytic SPP1 contributes to neurological dysfunction following cerebral ischemia through infarct-independent mechanisms.

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Poster

PSTR052: Stroke: Pathophysiology

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Program #/Poster #: PSTR052.04/W16

Topic: D.03. Stroke

Support: NINDS R01NS058784 (GKS)

Title: Spatial Bioenergetic Profiling Reveals Caloric Restriction Induced Changes in Mitochondrial Function After Ischemic Stroke

Authors: *M. KIM[1,3], V. GUPTA[1], X. LIANG[1], Y. MAEDA[1], T. BLISS[1], G. K. STEINBERG[2]; [1]Dept. of Neurosurg., [2]Stanford Univ., Stanford, CA; [3]Univ. of Virginia, Charlottesville, VA

Abstract: Brain function critically depends on mitochondrial oxidative metabolism, and impaired oxygen utilization is a hallmark of ischemic brain injury. While caloric restriction (CR) is known to influence brain metabolism, its effects on regional mitochondrial respiration following stroke remain poorly understood. Here, we applied an emerging fresh-tissue biopsy approach to spatially profile oxygen consumption rates in discrete brain regions following ischemic stroke in caloric restricted mice. Adult male C57BL/6 mice underwent three weeks of

CR or *ad libitum* (AL) feeding prior to 35-minute transient middle cerebral artery occlusion. Seven days post-stroke, tissue punch biopsies were collected from M1 motor cortex and striatum, in regions adjacent to the lesion core. Mitochondrial respiration was assessed using the Agilent Seahorse XF Cell Mito Stress Test, adapted for tissue biopsies. Seahorse respirometry revealed distinct region-specific bioenergetic profiles between CR and AL groups. Both striatum and cortex from CR mice exhibited significantly enhanced basal and ATP-linked respiration compared to AL controls. Notably, CR striatum additionally demonstrated significant improvements in maximal respiration and spare respiratory capacity, indicating superior mitochondrial reserve capacity. These findings suggest CR confers region-specific enhancement of mitochondrial function and resilience in the post-ischemic brain, with differential protective effects across brain regions. Our results demonstrate the utility of fresh tissue biopsy methodology for spatial metabolic profiling of brains and provide evidence that CR promotes a healthier mitochondrial microenvironment in the stroke-injured brain.

Disclosures: M. Kim: A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NINDS R01NS058784 (GKS). **V. Gupta:** A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA. **X. Liang:** A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA. **Y. Maeda:** A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA. **T. Bliss:** A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA. **G.K. Steinberg:** A. Employment/Salary (full or part-time):; Department of Neurosurgery and Stanford Stroke Center, Stanford University School of Medicine Stanford, CA 94305, USA.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.05/W17

Topic: D.03. Stroke

Support: NIH Grant RF1AG084134-01S1
NIH Grant L30AG089724
NIH Grant RF1AG084134

Title: Profile of pro-inflammatory cytokines in plasma following aneurysmal subarachnoid hemorrhage.

Authors: *E. SMITH[1], D. MERCURIO[1], T. A. UJAS[2], A. D. BACHSTETTER[2], B. NIKOLAJZCYK[3], A. M. STOWE[4], J. LUTSHUMBA[1];
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Abstract: Aneurysmal subarachnoid hemorrhage (aSAH) is a hemorrhagic stroke with many associated complications including vasospasm which typically occurs 4-14 days post stroke. Our previous studies profiled pro-inflammatory cytokines in the cerebrospinal fluid (CSF) and cultured peripheral blood mononuclear cells (PBMC) and found significant increases over time in all major inflammatory cytokines in the CSF, with IL-17 significantly increased in individuals who experienced vasospasm. Additionally, IL-1ß, IL-6 and TNF-α peaked at day 7 in PBMCs. To further characterize the profile of aSAH we measured these inflammatory cytokines in plasma. Samples were collected from patients (n=10) at 5 timepoints following onset of aSAH. Collections occurred on days 3, 5, 7, 10, and 14 post stroke. We measured inflammatory cytokines (IFN-γ, IL-10, IL-12p70, IL-1ß, IL-17, IL-2, IL-4, IL-6, TNF-α) using the S-Plex Proinflammatory Panel 1 (human) Kit from Meso Scale Discovery (MSD). Data were analyzed using a mixed-effects model comparing all patients together and vasospasm vs no vasospasm through Prism (vs 11.02). When comparing all patients, there was a significant increase in IL-1ß and IL-2 ($p=0.0339$, $p=0.0169$, respectively) between post-aSAH days 3 and 7. Both cytokines also demonstrated an overall upward trend across all timepoints. We found that levels of IL-10 and IL-2 showed significant change ($p=0.0440$, $p=0.0245$, respectively) over time in patients with regardless of vasospasm. IL-17 also experienced an overall upward trend ($p=0.086$) when looking at all patients combined. Inflammatory cytokines with significant changes across time appear to have a similar peak at day 7 as seen previously. IL-1ß, IL-2, and IL-17 contribute to post-aSAH systemic inflammation during the first 7 days. While IL-10 and IL-2 seem to play a role in the overall inflammatory response, since changes were seen equally between patients with and without vasospasm it is less likely that they would serve a role as biomarkers for risk of vasospasm, however, given the sample size we are not definitively powered to predict.

Disclosures: E. Smith: None. **D. Mercurio:** None. **T.A. Ujas:** None. **A.D. Bachstetter:** None. **B. Nikolajzcyk:** None. **A.M. Stowe:** None. **J. Lutshumba:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.06/W18

Topic: D.03. Stroke

Support: Chan-Zuckerberg Biohub Chicago Investigator Program
Chan-Zuckerberg Biohub Chicago SPARK Program
Beckman Institute of Advanced Science & Technology Graduate Fellows Program

Title: Circadian regulation of the blood-brain interface shapes vulnerability in ischemic stroke and aging

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Abstract: Ischemic stroke risk and severity exhibit pronounced circadian patterns, with incidence peaking in the early morning and nighttime, while stroke severity is often greater during the night. The mechanisms underlying this temporal vulnerability remain poorly understood. Emerging evidence suggests that circadian rhythms regulate the blood-brain interface (BBI), a critical barrier governing neurovascular integrity and inflammatory signaling. This research bridges circadian biology and stroke pathophysiology by testing whether circadian regulation of BBI permeability and neuroinflammation contributes to time-of-day-dependent stroke vulnerability. Circadian oscillations in pro-coagulant plasma proteins were assessed first, revealing rhythmic expression of fibrinogen, but not prothrombin. Cerebral microvessels were then isolated from rat brains at different times of day to quantify circadian variation in endothelial tight junction protein expression. To determine functional consequences, a photothrombotic ischemic stroke model was employed to induce focal, non-invasive neurovascular injury at defined circadian phases. Stroke outcomes were evaluated by measuring infarct size, BBI permeability, tight-junction disruption, coagulation markers, and neuroinflammatory responses. Together, these findings establish a direct relationship between circadian regulation of the BBI and ischemic stroke severity, identifying time-of-day-dependent vulnerability windows of neurovascular injury. This work provides mechanistic insight into how circadian control of vascular integrity and inflammation may influence stroke outcomes, with implications for aging and chronotherapeutic intervention.

Disclosures: S. Asif: None. **C. Deng:** None. **J.W. Mitchell:** None. **M.U. Gillette:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.07/W19

Topic: D.03. Stroke

Support: R01NS132794

Title: Investigating Brain Proteomic Changes in Hypertensive and Normotensive Mice after Intracerebral Hemorrhage

Authors: *K. SAIF, S. KELKAR, S. SUKUMARI RAMESH;
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Abstract: Intracerebral hemorrhage (ICH) is a life-threatening stroke subtype associated with high mortality and severe neurological deficits. Hypertension is one of the major risk factors for ICH and can worsen secondary brain injury. However, the pathophysiology of hypertensive ICH remains largely unknown. To gain insights, ICH was induced in hypertensive BPH/2J and normotensive BPN/3J male mice using the collagenase injection method. The ipsilateral and contralateral striatal brain tissues were collected on day 3 post-ICH and subjected to proteomic analysis using LC-MS/MS. Data-dependent acquisition (DDA) and data-independent acquisition (DIA) were carried out. The proteomic analysis identified 4064 and 1015 proteins using DDA and DIA, respectively. To determine brain injury-induced changes, quantitative analysis was performed, revealing 107 and 485 differentially expressed proteins (DEPs; $p < 0.05$) by DDA and DIA, respectively, between hypertensive ipsilateral and hypertensive contralateral brain samples post-ICH. Moreover, analysis of proteomic data from normotensive ipsilateral vs. normotensive contralateral tissue revealed 175 and 618 DEPs by DDA and DIA, respectively. DEPs included multiple 14-3-3 protein isoforms in both hypertensive and normotensive groups, implicating metabolic deregulation post-ICH. As per the bioinformatic studies, mitochondrial dysfunction, oxidative phosphorylation, glycolysis, oxidative stress, and inflammatory signaling were the prominent pathways associated with the DEPs. Also, hypertensive brain samples after ICH exhibited enhanced mitochondrial dysfunction compared with normotensive brain samples after ICH. Furthermore, DEPs from hypertensive and normotensive groups were compared with proteins associated with cognitive trajectory to explore potential links between post-ICH molecular alterations in the brain and cognitive outcomes. The analysis revealed several candidate proteins in both normotensive and hypertensive groups following ICH. Overall, these findings provide insight into brain protein-level changes associated with hypertensive ICH, and the dataset could help identify potential therapeutic targets.

Disclosures: K. Saif: None. **S. Kelkar:** None. **S. Sukumari Ramesh:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.08/W20

Topic: D.03. Stroke

Support: VA I01BX006894
VA IK6BX005647
WoodNext Foundation

Title: NCOA7 Deficiency Caused Lysosomal Dysfunction and Oligodendrocyte Loss, Exacerbating Post-Stroke White Matter Injury

Authors: *K. KALIYAPPAN[1,2,3], Y. SHI[4], A. JIANG[4], S. ROSE[5], A. PILLAI[1], P. PHADTARE[1], S. METWALLY[6], S. SONG[1], Y. TANG[4], V. FIESLER[1,2,3], S. CHAN[4], D. SUN[1,2,3];

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Abstract: Introduction: Ischemic stroke triggers profound white matter (WM) damage driven primarily by oligodendrocyte damage. Lysosomes are indispensable regulators of oligodendrocyte homeostasis, coordinating the lipid turnover, myelin recycling, and autophagic clearance, making lysosomal dysfunction a direct threat to oligodendrocyte survival and WM integrity [1]. Nuclear Receptor Coactivator 7 (NCOA7), a lysosome-associated regulator of V-ATPase assembly and lysosomal acidification, has been implicated in lysosomal homeostasis and its deficiency exacerbating pulmonary arterial hypertension (PAH) through lysosomal dysregulation and oxysterol accumulation [2], and associating with adverse WM changes in PAH populations [3]. We investigated how Ncoa7 deficiency in a knockout mouse model influences post-stroke outcomes. **Methods:** Adult wild-type (WT) and Ncoa7 knockout (Ncoa7-KO) mice (male and female) on a C57BL/6J background were subjected to transient middle cerebral artery occlusion (tMCAO) to model ischemic stroke. Post-stroke neurological deficits and brain pathology were evaluated using magnetic resonance imaging (MRI), histological analysis, and immunoblotting. **Results:** Ncoa7-KO mice exhibited significantly higher mortality, worsened neurological deficit and larger stroke infarction than WT mice, which was confirmed by in vivo T2 and ADC MRI-detection of increased infarct volume and edema. Histopathological analyses revealed heightened astrogliosis and microglial activation in Ncoa7-KO stroke brains. In addition, Ncoa7-KO stroke mice showed accelerated reduction in mature oligodendrocytes with a corresponding increase in OPCs in the corpus callosum compared to WT stroke mice. WM injury in Ncoa7-KO stroke mice was further confirmed by ex vivo diffusion tensor imaging and western blotting. Sustained lysosomal dysfunction of Ncoa7-KO stroke brains was reflected by reduced LAMP1 expression in neurons and oligodendrocytes. **Conclusion:** Ncoa7 deficiency increased post-stroke mortality and infarct volume in both sexes, likely driven by exacerbated neuroinflammation. WM integrity was significantly compromised in both stroke and non-stroke Ncoa7-KO brains, attributable to impaired oligodendrocyte maturation and sustained lysosomal dysfunction. These findings identify NCOA7 as a critical regulator of lysosomal integrity and WM resilience against stroke brain injury. Studying consequences of NCOA7 deficiency in WM cells and underlying cellular mechanisms is warranted.

Disclosures: K. Kaliyappan: None. **Y. Shi:** None. **A. Jiang:** None. **S. Rose:** None. **A. Pillai:** None. **P. Phadtare:** None. **S. Metwally:** None. **S. Song:** None. **Y. Tang:** None. **V. Fiesler:** None. **S. Chan:** None. **D. Sun:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.09/W21

Topic: D.03. Stroke

Support: Changchun GeneScience Pharmaceutical Co., Ltd.

Title: GenSci155, a Brain-Penetrant, Long-Acting IGF-1 Analog, Reduces Infarct Volume in a Rat tMCAO Model via the PI3K/AKT-mTOR-Autophagy Axis

Authors: *N. LIU, Y. CHEN, J. MA;
Translational Med., Changchun GenSci Pharmaceut. Co., Ltd., Shanghai, China

Abstract: <META NAME="author" CONTENT="liuna(刘娜)">**Title:** GenSci155, a Brain-Penetrant, Long-Acting IGF-1 Analog, Reduces Infarct Volume in a Rat tMCAO Model via the PI3K/AKT–mTOR–Autophagy Axis**Background:**Neuronal injury progresses rapidly after acute ischemic stroke, and effective neuroprotective therapies remain limited. Insulin-like growth factor-1 (IGF-1) promotes neuronal survival and tissue repair, but its short half-life limits translational application. GenSci155 is a fatty acid-conjugated, long-acting IGF-1 analog designed to enable albumin-mediated prolonged exposure and sustained activity. This study evaluated its brain lesion-targeting properties and neuroprotective mechanisms in preclinical stroke models.**Methods:**GenSci155 was evaluated in a rat transient middle cerebral artery occlusion (tMCAO) model. To assess biodistribution and retention in ischemic brain tissue, GenSci155 was radiolabeled with zirconium-89 (89Zr) and analyzed by positron emission tomography (PET). In vitro neuronal injury models were used to assess anti-apoptotic effects. Cerebrospinal fluid (CSF) samples from treated animals were analyzed by unbiased proteomics and pathway enrichment.**Results:**PET imaging showed that ^89Zr-labeled GenSci155 selectively accumulated in the ischemic lesion region of the ipsilateral hemisphere, with retention detectable up to 24 hours after administration, suggesting sustained exposure in injured brain tissue. In vitro, GenSci155 attenuated neuronal injury by inhibiting apoptosis. CSF proteomics suggested activation of the PI3K/AKT–mTOR pathway and suppression of autophagy-related signaling, potentially contributing to reduced neuronal apoptosis and infarct volume. Negative regulators of PI3K/AKT signaling, including SMAD3, PRKAB1, and MTMR7, and autophagy-related proteins TSC1, ULK1, and UVRAG were positively correlated with infarct volume and reduced after GenSci155 treatment. IGFBP-1, IGFBP-4, and IGFBP-5 were markedly upregulated, suggesting a feedback mechanism that may modulate IGF-1 bioavailability and support short-term neuroprotection.**Conclusion:**GenSci155 demonstrated sustained accumulation in ischemic brain lesions and neuroprotective activity in preclinical stroke models. Its effects may be mediated, at least in part, through modulation of the PI3K/AKT–mTOR–autophagy axis and inhibition of neuronal apoptosis. These findings support further development of GenSci155 as a potential neuroprotective therapy for acute ischemic stroke. GenSci155 has received clinical trial approval for AIS and is currently undergoing a Phase I clinical trial.

Disclosures: N. Liu: A. Employment/Salary (full or part-time):; Changchun GeneScience Pharmaceutical Co., Ltd. **Y. Chen:** A. Employment/Salary (full or part-time):; Changchun GeneScience Pharmaceutical Co., Ltd. **J. Ma:** A. Employment/Salary (full or part-time):; Changchun GeneScience Pharmaceutical Co., Ltd..

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.10/W22

Topic: D.03. Stroke

Support: R01AA030309
R01NS059962
R01NS083914

Title: Long-Term Neurological Consequences of Moderate Prenatal Alcohol Exposure: Oxidative Stress, STEP Dysfunction, and Stroke Vulnerability

Authors: *A. BHATTACHARJEE[1], S. CHOI[2], K. K. CALDWELL[3], C. F. VALENZUELA[4], R. PODDAR[5], S. PAUL[6];
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Abstract: Despite ongoing public health efforts, alcohol exposure during pregnancy remains common, influenced by social, biological, and contextual factors that shapes substance use. The effects of such prenatal alcohol exposure (PAE) on the offspring vary depending on the amount and frequency of drinking. While heavy or binge drinking during pregnancy is well known to increase the risk for Fetal Alcohol Spectrum Disorders (FASDs), the impact of moderate alcohol consumption on the offspring is not yet fully understood. Although, emerging evidence indicates that moderate PAE may lead to alteration in cerebrovascular function in the brain of the offspring, the long term consequences in adult offspring are not yet fully understood. Our findings in a mouse model of prenatal alcohol exposure (PAE) now demonstrate that in utero exposure to moderate levels of alcohol leads to significant depletion in the level of the major antioxidant, glutathione (GSH) in the brain of the offspring. We also found that the decrease in GSH level is associated with dimerization and subsequent loss of function of a brain-enriched and neuron specific tyrosine phosphatase, STEP. Since STEP is known to be involved in neuroprotection and increased oxidative stress down regulates STEP activity, the loss of function of STEP following moderate PAE could increase the vulnerability of the offspring to neurological insults in adulthood. Consistent with this interpretation, our findings further indicate that mild ischemic stroke induced by middle cerebral artery occlusion in adult PAE offspring worsens brain injury. The findings further show that a mild ischemic insult in moderate PAE mice triggers early onset and sustained activation of neuronal extracellular signal-regulated kinase mitogen-activated protein kinase (ERK MAPK), as well as increased phosphorylation of p38 MAPK, two members of the MAPK family that are substrates of STEP. This leads to degradation of Iκβ and rapid increase in the activation of neuronal NF-κB, and subsequent biosynthesis of the pro-inflammatory mediator prostaglandin E2 to worsen brain injury. Restoration of STEP signaling with intravenous administration of a novel STEP-mimetic peptide at the onset of reperfusion attenuates ischemic brain damage in PAE offspring. These findings suggest that impaired STEP function in moderate PAE mice contributes to the exacerbation of

ischemic brain injury by enhancing post-ischemic inflammatory response but also highlights the therapeutic potential of a STEP-mimetic in mitigating ischemic brain damage.

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Poster

PSTR052: Stroke: Pathophysiology

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.11/W23

Topic: D.03. Stroke

Support: NIH-R01NS126415
TAAF-Cerebrovascular Research Grant

Title: Endothelial VCAM1 mediates macrophage recruitment and intracerebral hemorrhage in mutant KRAS-induced brain arteriovenous malformations

Authors: *J.-E. PARK[1], H. PARK[1], O. MYINT[1], J. CHOI[4], S. JUNG[5], J. ARONOWSKI[2,3], P. CHEN[1], E. KIM[1], E. PARK[1,3];
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Abstract: Brain arteriovenous malformations (bAVM), tangled vessels, often cause intracerebral hemorrhages (ICH), resulting in high mortality and morbidity. Clinical evidence shows a high concentration of microglia/macrophages (MG/Mϕ) in both the unruptured and ruptured bAVM area, and we reported that MG/Mϕ-mediated inflammation is a critical driver of blood-brain barrier (BBB) loss and subsequent ICH. Although we previously demonstrated that the unruptured bAVM attracts Mϕ and increases inflammation, the mechanisms underlying Mϕ recruitment and BBB crossing in bAVM remain unknown. To interrogate the mechanism, we established a bAVM mouse model by overexpressing human mutant KRAS ($KRAS^{G12V}$) using an endothelial cell (EC)-specific AAV-BR1 vector (AAV-BR1-$KRAS^{G12V}$). Proteomic analysis of resected bAVM lesions from mutant KRAS-induced bAVM mice displayed significant upregulation of vascular cell adhesion molecule-1 (VCAM1) compared with intact brain regions. We validated the robust VCAM1 expression in the bAVM lesions, whereas the intact vessels showed minimal VCAM1 expression in mutant KRAS-induced bAVM mice. VCAM1 expression was significantly increased in ECs from both ruptured and unruptured human bAVM tissues compared with control arteries. We further confirmed that mutant KRAS significantly induced VCAM1 protein levels in cultured ECs transfected with $KRAS^{G12V}$. Here, we hypothesized that mutant KRAS in ECs recruits Mϕ *via* VCAM1 and enhances inflammatory responses in the bAVM area, thereby promoting hemorrhagic pathology. To test this hypothesis,

we first treated AAV-BR1-KRAS^{G12V}-injected *Cx3cr1-gfp;Ccr2-rfp* mice with a VCAM1 Neutralizing Antibody (VCAM1 NAb). In intravital imaging, we observed that VCAM1 NAb inhibited Mϕ infiltration and MG activation in the bAVM territory. To further test whether VCAM1 is responsible for Mϕ recruitment and bAVM rupture/ICH, we used *Cdh5-CreERT2;Vcam1$^{fl/fl}$* mice, in which tamoxifen-induced endothelial VCAM1 deletion significantly reduced Mϕ infiltration. Notably, VCAM1 NAb treatment or endothelial-specific VCAM1 knockdown attenuated Ter-119-positive red blood cell infiltration or bleeding, as identified by MRI. Taken together, our data suggest that VCAM1 modulates Mϕ recruitment to bAVM lesions and that VCAM1-mediated Mϕ infiltration contributes to ICH in bAVM mice.

Disclosures: J. Park: None. **H. Park:** None. **O. Myint:** None. **J. Choi:** None. **S. Jung:** None. **J. Aronowski:** None. **P. Chen:** None. **E. Kim:** None. **E. Park:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.12/W24

Topic: D.03. Stroke

Support: NIH Grant 1R01NS135153-01 (Dr. Kim)

Title: The role of CD44v6 in VEGF signaling and brain arteriovenous malformations

Authors: *O. MYINT[1], K. AYE[1], J. ARONOWSKI[2], P. R. CHEN[1], E. PARK[3], E. KIM[1]; [1]Neurosurg., UTHealth Sci. Ctr. at Houston, Houston, TX; [2]Neurol., Univ. Texas HSC - Houston, Houston, TX; [3]Dept. of Neurosurg., UTHealth Houston, Houston, TX

Abstract: Brain arteriovenous malformation (bAVM) is an abnormal tangle of vessels caused by the direct connection of arteries and veins without a capillary bed, which is a critical risk factor for brain hemorrhages. Current treatment options, including surgical resection, embolization, and radiosurgery, are often limited by the size, complexity, and eloquent location of the lesion, leaving many patients without effective or safe therapeutic alternatives. Brain endothelial-specific KRAS^{G12V} mutation causes bAVM development, in which excessive angiogenesis is the key feature. Vascular endothelial growth factor (VEGF) signaling, activated by VEGF-A binding to its receptor (VEGFR2), is critical in angiogenesis. CD44 variant isoform 6 (CD44v6) functions as a co-receptor for VEGFR2 and facilitates efficient VEGF signaling in endothelial cells. However, it is not clear how CD44v6 interacts with VEGF signaling and plays a role in bAVM pathology. We hypothesize that VEGF signaling is critical in bAVM formation, and CD44v6 intensifies VEGF signaling and exacerbates bAVM pathology. To test the hypothesis, we measured the expression and co-localization of VEGF-A, VEGFR2, and CD44v6 in human bAVMs and mouse bAVMs induced by endothelial-specific KRAS^{G12V} mutation. We also confirmed KRAS^{G12V}-induced bAVM formation and mortality rate in endothelial-specific VEGFR2-deficient mice (VEGFR2^{EKO}). The effect of CD44v6 inhibition on VEGF signaling

using CD44v6 siRNA was also tested in cultured endothelial cells overexpressing $KRAS^{G12V}$ (EC^{G12V}). We found higher expression levels of VEGF-A, VEGFR2, and CD44v6 in mouse bAVMs. $VEGFR2^{EKO}$ mice showed significantly reduced bAVM numbers/size, especially large bAVMs ($p<0.01$, n=8 mice/group), mortality rate ($p<0.0001$, n=18-20 mice/group), and improved nesting behavior ($p<0.01$, n=12-13 mice/group). VEGFR2 and CD44v6 colocalization was found in human and mouse bAVMs, which was decreased in bAVMs of $VEGFR2^{EKO}$. Additionally, CD44v6 siRNA significantly reduced VEGFR2 expression in EC^{G12V}. Taken together, we confirmed that VEGF signaling is critical in $KRAS^{G12V}$-induced bAVM pathology, and CD44v6 could regulate VEGF signaling. Our findings suggest that CD44v6 may contribute to bAVM development by regulating VEGF signaling. Further studies are granted to test the effect of CD44v6 inhibition in bAVM development.

Disclosures: O. Myint: None. **K. Aye:** None. **J. Aronowski:** None. **P.R. Chen:** None. **E. Park:** None. **E. Kim:** None.

Poster

PSTR052: Stroke: Pathophysiology

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Program #/Poster #: PSTR052.13/W25

Topic: D.03. Stroke

Support: NIH T32 (NS105607)
American Heart Association Career Development Award (#857344)
Colton Stroke Discovery Accelerator Grant
Brain & Behavior Research Foundation (#501451)

Title: Microglial Specific Epigenetic Regulation of Stroke Pathophysiology

Authors: *J. GROSS[1], H.-T. HUANG[2], S. PIETRZAK[3], I. GOLYNKER[1], K. MORRIS-BLANCO[4];
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Abstract: Ischemic stroke, caused by a blockage that reduces blood flow to the brain, is a leading cause of death and disability worldwide. Therapeutic advancements over the past decade have been limited, highlighting gaps in our understanding of stroke pathophysiology. Neuroinflammation is a key contributor to progressive brain damage after stroke, and microglia, the resident immune cells of the brain, are critical regulators of this process, contributing to both injury and repair processes. Epigenetic mechanisms, DNA modifications that regulate gene expression without altering the DNA sequence, guide microglial activation. Prior work identified the ten-eleven translocase 3 (Tet3) protein as a regulator of neuronal neuroprotective gene expression and stroke lesion size through conversion of the repressive mark 5-methylcytosine (5mC) to 5-hydroxymethylcytosine(5hmC), which is associated with increased gene expression.

However, the role of Tet3 in microglia remains unexplored, and its contribution to ischemic stroke pathophysiology is unknown. We hypothesize that Tet3 mediates microglial proinflammatory responses and 5hmC expression, thereby influencing stroke recovery and brain damage. To test this, we developed a conditional microglial-Tet3 knockout (P2ry12-Tet3cKO) mouse model and subjected male and female mice to middle cerebral artery occlusion to induce ischemic injury. We assessed outcomes at 3, 12, and 28 days post-stroke to capture acute injury, peak microglial activation, and longer-term repair. P2ry12-Tet3cKO mice of both sexes exhibited reduced neurological deficits, improved motor function, and enhanced body weight recovery compared to controls. However, only male P2ry12-Tet3cKO mice showed reduced lesion size at all time points, whereas females showed no change. Immunofluorescence of the P2ry12-Tet3cKO stroke mouse brain revealed sex differences in microglial Tet3 and 5hmC levels, and microglial inflammatory protein expression. These findings suggest that microglial Tet3 regulates sex-specific inflammatory and neuroprotective responses. Tet3 mediated genome modifications are reversible, highlighting their translational potential as therapeutic targets when combined with sex- and cell-type specificity.

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Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.14/W26

Topic: D.03. Stroke

Support: NIH R35NS132184

Title: Differential regulation of extrachromosomal circular DNA following ischemic Stroke in mice

Authors: *M. BAZAZ, R. VEMUGANTI;
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Abstract: Extrachromosomal circular DNA (eccDNA) is a heterogeneous class of small, circular DNA molecules derived from the nuclear genome. They emerged as novel regulators of gene expression and cellular stress responses. eccDNA were shown to modulate biological processes in cancer and aging. We presently profiled eccDNA abundance and composition in the periinfarct cerebral cortex of adult mice at 6h and 24h reperfusion following transient focal cerebral ischemia (middle cerebral artery occlusion; MCAO). The overall number of eccDNAs detected were not significantly altered at either reperfusion timepoint compared with sham. However, a discrete subset of 581 eccDNAs was commonly downregulated by atleast 6-fold at both reperfusion time points in the ischemic animals compared with sham. This included eccDNAs derived from B3galt5, Tacr2, Angpt4, and Camk2b genes. Conversely, eccDNAs

mapping to Grik1, Kcnk9, and Asic2 genes with established roles in neuronal excitability were upregulated with a 2.39 to 3.78 fold change at both 6h and 24h timepoints compared with sham. Several eccDNAs showed transient changes after ischemia (Socs1, Mad1l1, and Tiam1 were upregulated at 6h and Nenf, Synpo, Dpysl2, and Cacna1a were upregulated at 24h). Many of these are implicated in neuroprotection, cytoskeletal remodeling, and calcium signaling. Gene ontology enrichment analysis of differentially regulated eccDNAs revealed significant overrepresentation of biological processes such as antigen processing and presentation via MHC class I pathways, which were enriched specifically among upregulated eccDNAs at 24h, suggesting an activation of immune-associated genomic regions in the periinfarct cortex. These findings demonstrate that ischemic reperfusion induces a dynamic, temporally structured eccDNA response in the periinfarct cortex, with pathway enrichment pointing to both neuronal and immune mechanisms. Funded by US NIH and VA.

Disclosures: M. Bazaz: None. **R. Vemuganti:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.15/W27

Topic: D.03. Stroke

Title: Brain Endothelium: Non-Professional Phagocytes of the Blood-Brain Barrier

Authors: *M. RAI[1], R. CHANG[2], T. TRAN[2], A. KULKARNI[4], S. SHAH[2], K. RAMASAMY[2], R. SUMBRIA[3];
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Abstract: Background: Brain endothelial cells (BECs) of the blood-brain barrier (BBB), traditionally seen as structural barriers, function as non-professional phagocytes capable of erythrophagocytosis (EP). Our lab has shown that BECs phagocytose oxidatively stressed red blood cells (RBCs), modeled with tert-Butyl hydroperoxide (tBHP) to mimic aged RBCs, resulting in brain iron deposition without disrupting the BBB. This may be a new mechanism underlying cerebral microbleeds. However, the mechanisms regulating BEC-EP remain poorly understood. Further, whether BEC-phagocytosis (BEC-P) efficiency varies with cargo shape and size remains unknown. **Methods:** hCMEC/D3 (immortalized) and/or pHBMVEC (primary) human brain microvascular endothelial cells were used. The role of myosin-II contractility in BEC-EP was assessed by treating the hCMEC/D3 monolayer with blebbistatin, a myosin-II inhibitor, followed by co-incubation with fluorescently-labeled PBS- or tBHP-treated RBCs. BEC-EP was evaluated by myosin II immunostaining and confocal microscopy. Further, RBCs were aged *in vitro* by hypothermic storage (4°C) for 30 days, followed by co-incubation with the hCMEC/D3 monolayer. BEC-EP was confirmed via H&E staining, followed by imaging and quantification using ImageJ. Hypothermic aging-associated changes in RBC phosphatidylserine

(PS), CD47, and glycocalyx were assessed via Flow Cytometry. Finally, BEC's ability to phagocytose exogenous cargos was assessed by co-incubating hCMEC/D3 and pHBMVEC monolayers with fluorescently labeled zymosan A. bioparticles or polystyrene latex beads. BEC-P was assessed via confocal imaging, and 3D image rendering and quantification via Imaris. **Results:** Blebbistatin treatment significantly increased ($p<0.001$) BEC-EP of tBHP-RBCs with unaltered BEC viability ($p<0.05$). Hypothermic aging of RBCs significantly increased ($p<0.05$) BEC-EP and significantly decreased RBC glycocalyx ($p<0.05$) vs. freshly isolated RBCs. Imaris quantification showed cargo-specific BEC-P (tBHP-RBC>zymosan>latex beads), with cargo size and sphericity influencing the extent of internalization. **Conclusions:** These findings suggest that the acto-myosin cytoskeleton regulates BEC-EP. Further, RBC glycocalyx may be important in hypothermic RBC-aging-induced BEC-EP, implicating this phenomenon in blood transfusion safety. Finally, cargo-dependent heterogeneity was noted in BEC internalization, with cargo-specific properties (shape and size) differentially regulating BEC-P.

Disclosures: M. Rai: None. **R. Chang:** None. **T. Tran:** None. **A. kulkarni:** None. **S. Shah:** None. **K. Ramasamy:** None. **R. Sumbria:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.16/W28

Topic: D.03. Stroke

Title: Novel Chronic Stroke Model in Cynomolgus Monkeys

Authors: *Y. NAKAMURA, R. NISHIKATA, V. P. RUTH, K. SAWADA, K. HAYASHIDA; Shin Nippon Biomed. Laboratories, Ltd., Kagoshima-shi, Japan

Abstract: While numerous chronic stroke models have been established in rodents, reports in non-human primates (NHPs) remain limited. Moreover, many stroke models induce physical impairments severe enough to reach humane endpoints, thereby limiting long-term evaluation. This study aimed to establish a mild stroke model in cynomolgus monkeys that enables assessment during a chronic-like phase while minimizing physical impairment and allowing long-term maintenance. Transient occlusion of the middle cerebral artery (MCA) was induced using an ethyl ester of iodinated poppy-seed oil fatty acid as an embolic agent. Two animals were evaluated longitudinally for up to 28 days using magnetic resonance imaging (MRI) to assess ischemic lesions and the primate modified Rankin Scale to assess neurological function. In one animal, ischemia was induced in the hemisphere contralateral to the dominant hand; manual dexterity was assessed using the Modified Brinkman Board test, and corticospinal tract integrity was evaluated by diffusion tensor tractography (DTT). In this animal, performance on the Modified Brinkman board test remained below 20% of baseline and the DTT revealed a reduction of corticospinal tract fibers to 26.5% on the affected side along with a compensatory increase to 186.1% on the contralateral side at day 28. In both animals, decreased motor function

in the affected forelimb persisted up to 28 days, and ischemic lesions around the motor cortex were detected on diffusion-weighted MRI. Food intake recovered by day 2, and no significant body weight loss was observed up to 28 days. In conclusion, we established a transient MCA occlusion model in NHPs characterized by mild but sustained impairment, primarily affecting forelimb dexterity for at least 28 days. Although further studies are needed to evaluate inter-individual variability, this model enables assessment during a chronic-like phase of stroke with minimal impact on physical function and may serve as a valuable platform for translational stroke research.

Disclosures: Y. Nakamura: A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **R. Nishikata:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **V.P. Ruth:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **K. Sawada:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd. **K. hayashida:** A. Employment/Salary (full or part-time):; Shin Nippon Biomedical Laboratories, Ltd..

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.17/W29

Topic: D.03. Stroke

Support: IITP 2021-0-00742
KHIDI RS-2023-0026

Title: Memory recovery and white matter integrity in patients with chronic stroke: A two-year follow-up study

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[3]Rehabil. and Regeneration Res. Center, CHA Univ. Sch. of Med., Seongnam, Korea, Republic of

Abstract: Stroke is a major cause of cognitive impairment, including memory dysfunction. Although recovery is most pronounced during the subacute phase, memory function may continue to recover in the chronic phase, yet its longitudinal trajectory and structural correlates remain poorly understood. This study longitudinally characterized individual trajectories of memory function and white matter integrity of association tracts over 24 months in chronic stroke patients, and examined whether structural and functional changes follow a concordant temporal pattern. Six adults with unilateral chronic stroke (≥6 months post-onset; median age 64 [IQR 60-67] years) were enrolled. Assessments were conducted at baseline (T0), 12-month (T1), and 24-month (T2) follow-up. Memory function was evaluated using the Rey-Kim Memory Test

(RKMT; Memory Quotient, MQ). DTI was performed on a 3.0 Tesla scanner at all three time points. Fractional anisotropy (FA) was extracted from five ipsilesional association fiber tracts (SLF, IFOF, UF, CGC, CGH) using the JHU ICBM-DTI-81 atlas. Longitudinal changes were assessed using the Friedman test. Median RKMT MQ increased from 66.5 [60.5-80.0] at T0 to 93.0 [76.3-101.5] at T2 (Friedman test, $p = 0.020$), with considerable individual variability. FA across all five ipsilesional association fiber tracts showed no significant longitudinal changes (all $p > 0.05$), with heterogeneous patterns across tracts and participants. Memory recovery was observed in chronic stroke patients, whereas ipsilesional association tract FA values did not show consistent longitudinal changes. These findings suggest that functional recovery and white matter integrity may follow dissociable trajectories during the chronic phase. Larger longitudinal studies are warranted to clarify network-level mechanisms underlying late-phase memory recovery.

Disclosures: Y. Kim: None. **H. Kim:** None. **S. Shin:** None. **M. Kim:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.18/W30

Topic: D.03. Stroke

Support: NIH (NIDCD) T32DC019481
MedStar National Rehabilitation Network
NIH (NIDCD) R01 DC014960
NIH (NIDCD) R00 DC018828

Title: A contralesional right hemisphere does not generally become more left hemisphere-like after stroke

Authors: *T. K. M. DAY, N. VLADYKO, A. T. DEMARCO, P. E. TURKELTAUB; Georgetown Univ., Washington, DC

Abstract: The reorganization of the contralesional hemisphere following a stroke is an active area of work, with a specific focus on how it relates to better behavioral outcomes. Prior work demonstrated that hemisphere chirality can be identified based on within-hemisphere functional connectivity patterns. Using linear discriminant analysis, a “hemisphere score” can be calculated for each hemisphere, representing how (dis)similar it is from the prototypic hemisphere. The distinctiveness between a person’s hemispheres varies, and is lower in left-handed individuals. One prediction is that strokes increase activation of homotopic areas, e.g., left-hemisphere (LH) strokes would result in a right hemisphere (RH) that is more “LH-like.” We applied a similar method to individuals with LH strokes (LHS; n = 96; 35 - 92 y) and age-matched healthy controls (n = 69; 31 - 84 y). We first classified patient status from only within-RH connectivity using the Brainnetome atlas; and second, we performed a three-way classification between control LH/RH or LHS RH. Patient status was predicted from RHs with an accuracy of 70%,

with larger lesions leading to a greater likelihood of being correctly predicted, odds ratio [log10(lesion volume)] = 2.9. The overall accuracy of the three-way prediction was 87%, including detecting the correct patient status 88% of the time; and correctly labeling the stroke RH 100% of the time. However, the majority of LHS participants showed RHs that were more "RH-like" than "LH-like," and more RH-like than the controls ($d = -0.8$, $t = -4.6$, $p < .001$). An increasing number of lesioned language regions did not predict LH-likeness ($\beta = 0.03$, $p = .06$), and lesion volume did not affect the hemisphere score ($p = .4$). However, hemisphere score was marginally associated with aphasia quotient ($B = -0.17$, $p = .04$). That is, individuals with worse aphasia symptoms had hemispheres that were more RH-like, rather than more LH-like. There was a marginal moderation ($p = .08$) of brain organization on the relationship between log lesion volume and aphasia quotient; for lesions larger than 10 cm3, an RH that is more LH-like has better aphasia outcomes than a contralesional hemisphere that is more RH-like. We find no large-scale reorganization toward a LH-like pattern in contralesional RHs; including in those that had strokes affecting more of the language network. We find greater changes in RH organization following larger strokes, and that greater re-organization likely does not reflect better behavioral recovery following similarly sized strokes. However, this analysis is cross-sectional and does not account for longitudinal change.

Disclosures: T.K.M. Day: None. **N. Vladyko:** None. **A.T. Demarco:** None. **P.E. Turkeltaub:** None.

Poster

PSTR052: Stroke: Pathophysiology

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.19/X1

Topic: D.03. Stroke

Support: R21 AG068802-01
RF1 AG079324

Title: Frequency-Specific Neurophysiological Functional Connectivity Relates to Behavioral Outcomes Following Minor Stroke

Authors: *V. COMMURI[1], I. DALLASTA[2], S. LARSON[1], J. Z. SIMON[2], E. B. MARSH[1]; [1]Dept. of Neurol., Johns Hopkins Sch. of Med., Baltimore, MD; [2]Electrical and Computer Engin., Univ. of Maryland, Col. Park, College Park, MD

Abstract: Individuals with minor stroke exhibit impairment along a variety of neurocognitive dimensions. Specific deficits are known to present with pronounced effects within particular neurophysiological frequency regimes, with aberrations in the beta band, for example, linked to impaired motor function. This study relates several clinical behavioral measures commonly used to predict recovery with band-specific neurophysiological functional connectivity obtained from participants' brief resting-state magnetoencephalography (MEG).

We apply the Network Localized Granger Causality (NLGC) framework to one minute-long resting state scans from a cohort of 70 individuals with minor stroke at two clinical visits. NLGC functional connectomes are derived for each of the canonical frequency bands (delta, theta, alpha, beta, gamma) and are related to behavioral measures using a whole-connectome mixed-effects regression analysis. Cluster testing and counterfactual modeling are used to establish the significance of the results.
The results show significant associations between patterns of neurophysiological functional connectivity and behavioral outcomes. These relationships exhibit frequency-specific organization, suggesting that different neurophysiological networks capture distinct aspects of post-stroke impairment and recovery. Longitudinal elements included in the models show how band-specific neural connectivity relates to favorable and unfavorable recovery across clinical visits.
We demonstrate the utility of MEG in characterizing post-stroke functional network organization. The scan duration brevity combined with its power in relating quantitative neural measures to behavioral outcomes may encourage broader clinical applications of advanced electrophysiological source analyses to support recovery monitoring and inform rehabilitation strategies.

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Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.20/X2

Topic: D.03. Stroke

Support: 2T32HD007414-31
P50 DC014664
R01 DC05375
P41 EB031771
1S10OD021648

Title: Vascular territory, not hemispheric bilaterality, shapes language outcomes after bilateral stroke

Authors: *M. J. MARTE[1], J. C. GUDENKAUF[1], A. V. FARIA[1], M. D. STOCKBRIDGE[2], A. E. HILLIS[3];
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Abstract: Bilateral cerebral hemispheric stroke accounts for roughly 5%-12% of all clinical stroke admissions yet is routinely excluded from language research on the basis of lesion laterality alone. This exclusion rests on an untested assumption that bilateral damage is a more

severe case of unilateral damage, even as recent work suggests these patients show some of the greatest heterogeneity in post-stroke recovery. To our knowledge, whether bilaterality independently worsens language outcome has never been tested at scale. We characterized acute language outcomes in 184 patients with left-hemisphere or bilateral stroke (159 left, 25 bilateral) using the Western Aphasia Battery-Revised (WAB-R), lesion quantification across language network parcellations, and vascular territory mapping. Counterintuitively, patients with bilateral lesions scored higher than patients with only left hemisphere lesions on the WAB Aphasia Quotient (mean 87.8 vs. 73.9). This largely reflected vascular territory: bilateral lesions were disproportionately watershed relative to the unilateral left-hemisphere cohort (40% vs. 3% of lesion volume), accumulating volume while sparing the canonical language network (mean left language-region load 5.4 vs. 11.2 mL). Controlling for left language network lesion load, bilateral status contributed no independent effect. A regression including lesion data explained 44.9% of WAB variance in left-hemisphere patients but only 6.8% in bilateral patients. Unsupervised clustering of lesion anatomy revealed two large discrete bilateral subtypes, a watershed pattern and a subcortical (lenticulostriate/thalamic) pattern, and a smaller ACA-centric subtype. Language outcomes after bilateral stroke thus appear governed by left perisylvian network load, as in unilateral stroke, not by bilaterality. Because the WAB-R is most sensitive to left middle cerebral artery perisylvian syndromes, it may under-detect deficits from watershed, subcortical, ACA territory or right-hemisphere injury. These findings motivate territory-based rather than laterality-based inclusion criteria, and complementary assessment approaches beyond the standard aphasia battery, in stroke language research.

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Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.21/X3

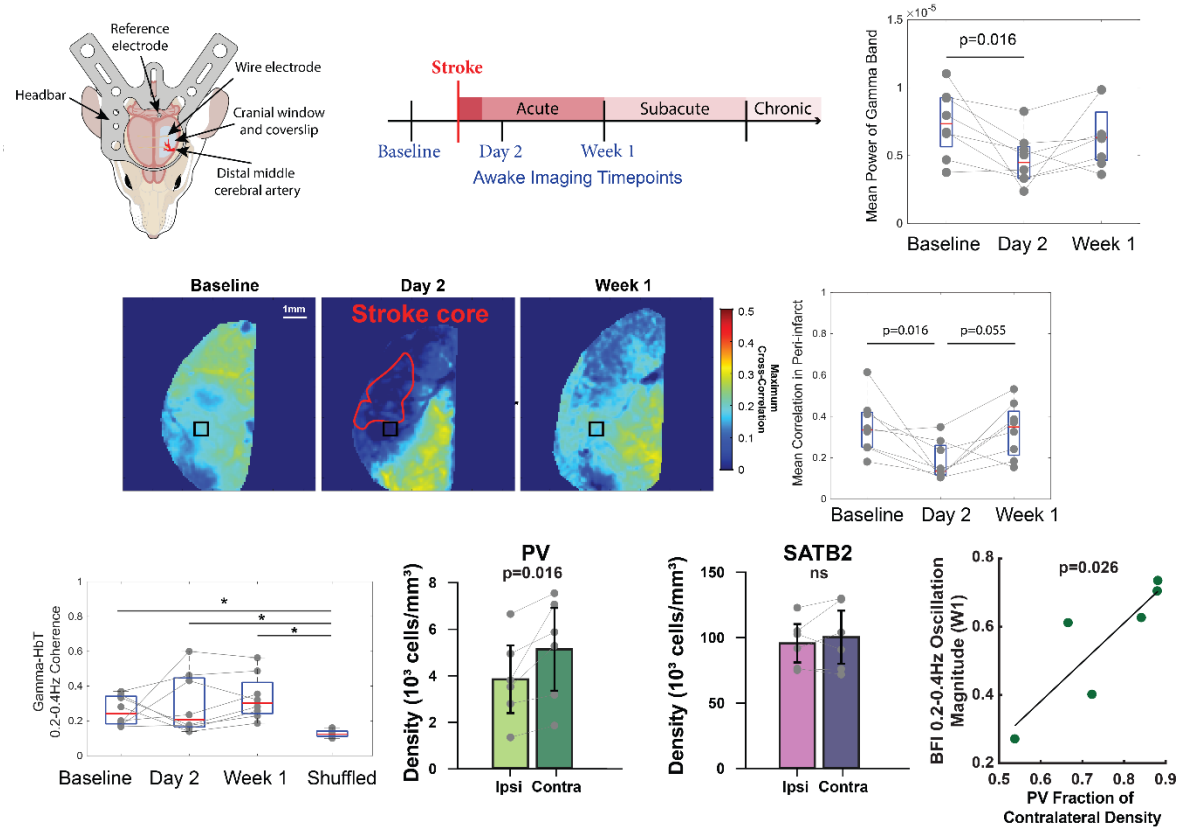
Topic: D.03. Stroke

Support: NIH Grant R01NS127156
NIH Grant R01NS122742

Title: Post-stroke oscillatory and aperiodic neural activity changes are reflected in hemodynamics and neurovascular coupling

Authors: *R. TANG[1], E. LONG[1], J. JIANG[1], M. SIMKULET[1], E. ERDENER[3], K. HERREMA[1], T. M. O'SHEA[1], M. THUNEMANN[2], A. DEVOR[2], D. A. BOAS[2]; [2]Biomed. Engin., [1]Boston Univ., Boston, MA; [3]Norolojik Bilimler ve Psikiyatri Enstitusu, Hacettepe Univ., Ankara, Turkey

Abstract: Neurovascular changes after ischemic stroke are complex and involve damage and repair in different cell populations, which affect neural activity and hemodynamics. These changes, such as increased low frequency vascular oscillations and interhemisphere gamma band asymmetry, have been correlated with behavioral recovery. However, the post-stroke alterations in cross-frequency neurovascular coupling and the specific cell types and frequency bands that could explain these alterations and their relation to behavioral recovery has not been fully elucidated. In this study, we investigated the relationship between neural changes and hemodynamics in a mouse model of ischemic stroke. First, we simultaneously measured hemodynamics (Δ[HbT]) and local field potential (LFP) before and at 2 and 7 days after photothrombosis (n=8 wild-type C57Bl/6). Gamma-band (30-150Hz) power was diminished at 2 days post-stroke (p=0.016), and low frequency Δ[HbT] oscillations were increased at 2 and 7 days post-stroke. Neurovascular coupling between gamma-band activity and Δ[HbT] was diminished at 2 days but partially recovered by 7 days. Interestingly, a significant coherence between delta band (2-4Hz) and 0.1-0.3Hz vascular oscillations emerged after stroke. Immunohistochemistry at 7 days showed that the density of parvalbumin (PV) neurons was decreased in the peri-infarct compared to the contralateral hemisphere (p=0.016), potentially explaining disruptions of gamma. Larger PV neuron density was associated with greater vascular oscillation power (VOP) at 7 days (p=0.026). Finally, the aperiodic exponent of the LFP spectrum was significantly correlated with the VOP at all timepoints, where animals with more high-frequency content had greater VOP. In summary, these results suggest that changes in VOP may indicate neural changes in PV neurons and changes in oscillatory (delta, gamma) and aperiodic components of the LFP.



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Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.22/X4

Topic: D.03. Stroke

Title: Pathology-Derived SVD Proxies Show Coherent Associations with Antemortem WMH Burden in NACC

Authors: *A. D. GONZALEZ[1], M. DONG[2], B. E. DANNER[5], A. GHASEMINEJAD-BANDPEY[2], S. BRANDIGAMPALA[3], S. SESHADRI[2], M. HABES[6], S. ETEMADMOGHADAM[4], M. E. FLANAGAN[2];
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Abstract: Current methods for evaluating cerebrovascular pathology are unstandardized and capture limited aspects of pathology. This gap has limited the ability to accurately model mixed dementias and directly assess the impact of cerebrovascular pathology on cognitive impairment. We previously developed a harmonized framework that adapts two well-accepted indices — scaled small vessel disease (SVD) burden and the Vascular Cognitive Impairment Neuropathology Guidelines-Lite (VCING-Lite) — for use with large-scale neuropathology (NP) cohorts. Here, we evaluate the associations between pathology-derived proxies and antemortem MRI white matter hyperintensity (WMH) and lesion burden metrics. We identified National Alzheimer's Coordinating Center (NACC) participants with both neuropathology form version 11 (NP11) data and antemortem MRI, yielding 151 cases. WMH size, Voxels, count, and distribution were assessed individually and summarized as case-level means and medians. Spearman correlations assessed associations between scaled SVD burden, six pathology domain scores, and WMH metrics; Kruskal-Wallis tests evaluated WMH differences across VCING-Lite categories. Scaled SVD burden correlated positively with all five WMH metrics ($\rho = 0.33$-0.34, all $p < 0.0001$). Arteriolosclerosis was the strongest domain-level correlate, particularly for periventricular lesion count ($\rho = 0.39$, $p < 10^{-6}$), while white matter rarefaction showed the strongest association with periventricular WMH volume ($\rho = 0.33$, $p < 0.0001$). VCING-Lite categories significantly stratified WMH burden across all metrics ($p = 0.0006$-0.011), with lesion counts increasing monotonically from Low to High severity. In contrast, WMH volumes showed a non-monotonic pattern, with the Intermediate category exceeding the High category. Results were robust to analytic choices (mean- vs. median-based correlations: $\Delta\rho \leq 0.005$). NP11-

derived SVD burden and VCING-Lite show coherent, mechanistically plausible associations with antemortem WMH burden, providing cross-modal validation for these harmonized proxies. The periventricular predominance of arteriolosclerosis associations aligns with deep perforator arteriopathy, while non-monotonic WMH volumes across VCING-Lite categories suggest high-burden cases reflect lesion heterogeneity rather than larger confluent hyperintensities. These findings support the use of NP11-derived indices as pathology anchors for imaging translation, offering a scalable framework for disentangling cerebrovascular contributions to cognitive impairment in mixed dementia research.

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Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.23/X5

Topic: D.03. Stroke

Title: A novel microRNA-Mediated Regulatory Mechanism of Ferroptosis After Subarachnoid Hemorrhage

Authors: *R. OTSUKA[1], T. IKEDO[1], W. YOSHIZAKI[1], Y. MINEHARU[1], K. YASUDA[2], T. MAKI[2], T. HORIE[3], K. ONO[3], Y. ARAKAWA[1];
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Abstract: Early brain injury (EBI) is a major determinant of poor neurological outcome after subarachnoid hemorrhage (SAH). Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation and iron accumulation, has emerged as a key contributor to EBI, but its upstream regulatory mechanisms remain poorly understood. MicroRNA-33 (miR-33) is a lipid metabolism-regulating microRNA; however, its role in ferroptosis after SAH is unknown. We hypothesized that miR-33 regulates ferroptosis by coordinating lipid and iron homeostasis after SAH. Cerebrospinal fluid (CSF) samples were obtained from patients with aneurysmal SAH (n=5) and unruptured intracranial aneurysms (n=3). An experimental mouse model of SAH was induced using a prechiasmatic autologous blood injection model in adult male C57BL/6J wild-type (WT) mice and miR-33 knockout (KO) mice. Survival, modified Garcia score, brain water content, neuronal degeneration, lipid peroxidation, Fe^{2+} accumulation, ApoE expression, and ferroptosis-related signaling were evaluated 24 h after SAH. The therapeutic effect of miR-33 inhibition was evaluated by simultaneous administration of an antisense oligonucleotide (ASO) into the prechiasmatic cistern at the time of SAH induction. Human cerebrospinal fluid (CSF) miR-33a levels were elevated in patients with SAH and

positively correlated with clinical severity, suggesting a role for miR-33 signaling after SAH. In a mouse model of SAH, miR-33 KO mice showed improved survival (93% vs. 55%, log-rank p=0.025), neurological function (modified Garcia score, 16/18 vs. 9/18), and reduced brain edema (brain water content, 55% vs. 64%) compared with WT mice. Fluoro-Jade C-positive degenerating neurons were reduced by about 50% in KO mice. Ferroptosis-associated lipid peroxidation was attenuated in KO mice, as demonstrated by lower lipid hydroperoxide levels (182±15 vs. 219±23 nmol/g) and malondialdehyde levels (1.8±0.9 vs. 4.1±0.9 nmol/mg). Lipid metabolic analysis revealed decreased expression of the pro-ferroptotic enzyme LPCAT3 and increased expression of the anti-ferroptotic enzyme ACSL3 in KO mice. Fe^{2+} levels were reduced (12.3±0.4 vs. 18.5±3.6 nmol/g), whereas ApoE levels were increased (53.0±1.9 vs. 34.6±0.6 ng/g). ASO-mediated inhibition of miR-33 recapitulated the neuroprotective phenotype and improved neurological outcomes after SAH. These findings identify miR-33 as a novel regulator of ferroptosis after SAH. By coordinating ApoE-associated iron homeostasis and ferroptosis-related lipid metabolism, miR-33 integrates multiple injury mechanisms and may represent a promising therapeutic target for EBI after SAH.

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Poster

PSTR052: Stroke: Pathophysiology

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.24/X6

Topic: D.03. Stroke

Support: EDR Team Science Award AWD-ImmunoInfl-TSA

Title: Stroke-associated pneumonia amplifies pathological brain-lung axis dysfunction

Authors: *E. D. CABRERA RANALDI[1], A. VILLABONA-RUEDA[2], J. SANCHEZ-MOLANO[3], W. J. MORENO[3], W. M. WALTERS[3], M. GILSON[3], O. UMLAND[4], W. DIETRICH, III[3], F. D'ALESSIO[2], N. KERR[3];
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Abstract: Stroke ranks as the second leading cause of mortality worldwide and constitutes a significant source of lifelong disability. Among patients who survive the acute phase post-stroke, 30% develop stroke-associated pneumonia (SAP). The emergence of SAP is correlated with markedly increased mortality and comorbidity rates. The post-stroke period is characterized by considerable variability in the peripheral immune response, which may predispose patients to infections. Conventional pneumonia treatments often fail in vulnerable stroke patients, highlighting the need for an experimental SAP model to study immune mechanisms and develop

novel therapies. To better understand how the brain-lung axis affects susceptibility to pneumonia and to exacerbated SAP complications, we used the photothrombotic mouse model of stroke (PTS) to induce a reproducible and clinically relevant ischemic brain injury. 5-month-old mice (n = 10/group) underwent PTS in the dorsal parietal cortex or sham surgery. 24 hours after PTS, mice were infected with *Streptococcus pneumoniae* ($2.5x10^6$ colony forming units [CFU]) *via* intratracheal instillation; controls were administered PBS. Histological grading of lung injury and cerebral ischemic insult were determined 8-days after stroke. To characterize pneumonia infection, bronchoalveolar lavage fluid (BALF) was collected at 7-days for cytological analysis and CFU counts. Whole lung, brain tissue, and BALF, were examined for immune landscape dynamics using flow cytometry. Our findings demonstrate that stroke-associated pneumonia (SAP) amplifies injury across the brain-lung axis, increasing cerebral infarct size, worsening lung injury, and promoting pulmonary inflammatory cell infiltration. Further, we found that SAP mice had increased neutrophils, lymphocytes, and total cell count in the BALF. Notably, there were several marked increases in plasma inflammatory cytokine concentrations in the plasma of SAP mice when compared to stroke-PBS controls, specifically in interleukin (IL)-1β (0.012), tumor necrosis factor-α (0.043), IL-6 (0.004), and interferon-γ (0.016) concentration (pg/mL), indicating marked systemic immune activation. Together, these data identify SAP as a driver of maladaptive brain-lung crosstalk that exacerbates tissue injury, disrupts immune homeostasis, and impairs the resolution of inflammation. This clinically relevant model provides a valuable platform to define underlying mechanisms and develop targeted therapeutic strategies.

Disclosures: E.D. Cabrera Ranaldi: None. **A. Villabona-Rueda:** None. **J. Sanchez-Molano:** None. **W.J. Moreno:** None. **W.M. Walters:** None. **M. Gilson:** None. **O. Umland:** None. **W. Dietrich:** None. **F. D'Alessio:** None. **N. Kerr:** None.

Poster

PSTR052: Stroke: Pathophysiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR052.25/X7

Topic: D.03. Stroke

Support: Merit Review Award Number 1I01BX006223-01A1 from the U.S. Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service
Merit Review Award Number I01 RX003506 from the U.S. Department of Veterans Affairs Rehabilitation R&D (RR&D) Service
Florida Department of Health #25K06
American Heart Association (AHA; 25TPA1476464)

Title: Oral contraceptive exposure impairs post-stroke cognition and dysregulates sphingolipid signaling in female rats

Authors: *A. I. RAMOS[1], S. SHARMA[1], I. CABEDA DIAZ[1], A. P. RAVAL[1,2,3];
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Abstract: Combined estrogen-progesterone oral contraceptives (OCs) are the most widely used form of contraception and are associated with an increased risk of ischemic stroke, particularly during the first year of use. OC exposure has also been linked to altered cognitive and emotional responses, yet the mechanisms by which OCs influence stroke outcomes remain poorly understood. We investigated the effects of short- and long-term OC exposure on post-stroke cognitive outcomes and cerebral sphingolipid metabolism in female rats. Adult Sprague-Dawley female rats (n=8/group) received placebo or OC treatment for 4-6 or 12-14 estrous cycles. Animals were randomly assigned to two cohorts. The first underwent transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery and survived for 21 days before behavioral and histological assessments. The second cohort was used for unbiased global metabolomic profiling (Metabolon Inc.), complemented by Western blotting, microglial morphological analyses, and enzyme activity measurements. Pathway enrichment analysis identified significant alterations in sphingolipid metabolism following OC exposure. Levels of sphingosine-1-phosphate (S1P), a bioactive lipid involved in synaptic transmission, neuroinflammation, and neuronal survival, were significantly elevated in OC-treated brains compared with placebo controls ($p<0.05$). OC exposure was also associated with increased expression of sphingosine kinase-2 (SphK2) and sphingosine-1-phosphate receptor-3 (S1PR3) protein and gene expression, accompanied by reduced expression of S1P lyase (S1PL), suggesting enhanced S1P signaling in OC-treated animals. Given the established role of S1PR3 in regulating microglial activation and neuroinflammatory responses, these findings implicate dysregulated sphingolipid signaling as a potential mechanism linking OC exposure to adverse neurological outcomes. OC exposure alters cerebral sphingolipid metabolism by enhancing S1P signaling pathways associated with neuroinflammation. These OC-induced changes may contribute to increased vulnerability to ischemic injury and post-stroke cognitive impairment. Understanding the impact of OC-induced sphingolipid dysregulation may provide novel insights into stroke risk and neurological outcomes in women using hormonal contraception.

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Poster

PSTR052: Stroke: Pathophysiology

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Topic: D.03. Stroke

Support: Merit Review Award Number 1I01BX006223-01A1 from the U.S. Department of Veterans Affairs Biomedical Laboratory R&D (BLR&D) Service
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Florida Department of Health #25K06
American Heart Association (AHA; 25TPA1476464)

Title: Menopausal transition modeled by VCD impairs cognitive recovery and worsens stroke outcomes

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Abstract: Menopausal transition-associated declines in circulating estradiol-17β (E2) reduce neuroprotection, thereby increasing both the risk and severity of ischemic stroke (IS). This heightened vulnerability underscores the need for physiologically relevant experimental models;however, commonly used models such as aging and ovariectomy fail to accurately recapitulate the gradual hormonal changes of the menopausal transition. Recent studies demonstrate that treatment with 4-vinylcyclohexene diepoxide (VCD) induces ovarian failure by selectivelydepleting primordial and primary follicles, thereby mimicking key features of the menopausal transition. Importantly, this approach avoids confounding effects of aging and the abrupt loss of E2 associated with surgical ovariectomy. Accordingly, we aimed to characterize the VCD-induced rat model of menopause and evaluate its impact on post-stroke ischemic injury, as well as motor and cognitive outcomes. Adult female Sprague-Dawley rats treated with VCD (80 mg/kg/day, intraperitoneal) or vehicle (peanut oil) for 20 days underwent transient middle cerebral artery occlusion (tMCAO; 90 minutes) and were followed for 21 days, after which behavioral testing and tissue collection were performed. Motor function was assessed using the cylinder test at baseline and 7 days post-tMCAO. Cognitive performance was evaluated using the Morris water maze during the final 7 days of the study, followed by histological and immunohistochemical analyses. Overall, results indicate that VCD treatment exacerbates post-stroke cognitive deficits and increases infarct volume.

Disclosures: I. Rodriguez: None. **I. Cabeda Diaz:** None. **A.P. Raval:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.01/X9

Topic: D.04. Brain Injury and Trauma

Support: University of Miami Neuroscience Team Science award
The Buoniconti Fund
The Miami Project to Cure Paralysis

Title: Effects of Oxycodone Exposure after Mild Traumatic Brain Injury

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Abstract: Chronic pain is a common, debilitating symptom after traumatic brain injury (TBI). Oxycodone is often prescribed for chronic pain after TBI, but whether oxycodone impacts recovery from TBI is not well understood. Prior studies have found that oxycodone use after mild TBI (mTBI) increases drug-seeking behavior and neuroinflammation characterized by increased Iba-1 positive microglia. Thus, we hypothesized that mTBI modifies the severity of opioid withdrawal and related emotional and cognitive behaviors after chronic oxycodone use. To test this hypothesis, we characterized affective and cognitive outcomes following mild controlled cortical impact (CCI) and post-injury chronic oxycodone exposure. Male and female C57BL/6J mice received sham or mild CCI surgery followed by escalating oxycodone doses (10-50 mg/kg, s.c.) or saline twice daily for nine days. Behavioral assessments included spontaneous withdrawal testing, open field test, sociability test, tail suspension test, and fear conditioning. Mice subjected to mTBI and oxycodone exposure exhibited lower withdrawal severity compared to sham oxycodone-treated mice (interaction of surgery × drug treatment, $F(1,89)=7.216$, $p=0.0086$, n=20-26/group). Oxycodone treatment reduced time spent in the center of the open field (main effect of treatment, $F(1,75)=12.45$, $p=0.0007$, n=19-20/group) and increased social avoidance (main effect of treatment, $F(1,22)=21.37$, $p=0.0001$, n=6-9/group), independent of injury. No significant effects were observed in the tail suspension test or between male and female mice in these measures. These findings indicate that mTBI modulates opioid withdrawal symptoms while oxycodone exposure selectively affects anxiety- and social-related behaviors.

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Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.02/X10

Topic: D.04. Brain Injury and Trauma

Support: NIH T32 AG020494

Title: Evaluating the neuropathogenic role of CD8 T-cells in traumatic brain injury using the closed head impact model of engineered rotational acceleration

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Abstract: Traumatic brain injury (TBI) is cerebral damage resulting from a blow to the head, affecting over 60 million individuals worldwide each year. Common causes such as motor vehicle accidents and falls can lead to diffuse axonal injury (DAI), characterized by stretching and shearing of axons following the rapid acceleration and deceleration of the brain. Increasing evidence suggests that chronic neuroinflammation in response to this damage contributes to the development of a secondary injury. Among the immune cells implicated in this process, CD8 T-cells have emerged as important contributors to TBI neuropathology; however, their precise functional role in TBI pathophysiology and long-term outcomes remains understudied. This persistent and often underrecognized inflammatory process has contributed to TBI being described as a "silent epidemic," characterized by chronic motor, cognitive, sensory, and affective symptoms that continue to impair recovery for millions worldwide. Therefore, uncovering the underlying mechanisms of TBI neuropathology is essential for the development of effective pharmacological interventions aimed at preventing long-term neurological deficits. In this study, we investigated the role of CD8 T-cells in TBI using 8-week-old male C57BL/6 and CD8 alpha chain knockout (*CD8a*^{tm1Mak}) mice (n=14 per group). Mice were lightly anesthetized and mild TBI was induced using the closed-head impact model of engineered rotational acceleration (CHIMERA), with mice receiving two impacts 24 hours apart. Sham mice were lightly anesthetized but received no impact. Animals were then laid supine in a recovery cage and assessed for latency to regain their righting reflex. Animals then underwent an eight-week behavioral testing regimen evaluating motor, sensory, cognitive, and affective function performed by blinded experimenters. Following injury, TBI mice showed significantly higher latencies to regain their righting reflex compared to sham mice, with no differences across strains. Deficits in associative learning and long-term memory were found in both mouse strains. However, wildtype mice exhibited other, more pronounced impairments compared to the *CD8a*^{tm1Mak} mice, including mechanical allodynia, transient motor deficits, and impairments in memory consolidation and procedural learning. This suggests that the presence of CD8 T-cells plays a deleterious role in TBI-induced dysfunction. Overall, these findings support further investigation into the mechanisms by which CD8 T-cells contribute to TBI neuropathology and may inform the development of immune-targeted therapeutic strategies aimed at mitigating long-term impairment.

Disclosures: N. Jones: None. **S.B. Ortega:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.03/X11

Topic: D.04. Brain Injury and Trauma

Support: VA MERIT I01RX003498
BLR&D I01BX006511-01

Title: Cognitive assessment following TBI with Fronto-hippocampal dependent memory tasks in pigs

Authors: ***S. PENNACCHI**[1], E. MIRZAKHALILI[2], E. R. HALTER[2], M. ROSALINO[1], B. MCCULLOUGH[3], J. A. WOLF[4];
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Abstract: We have designed and adapted a battery of cognitive tasks, including two touchscreen tasks and the delayed alternating T-maze, with the primary aim of assessing behavioral changes post-traumatic brain injury (TBI). These paradigms were tested in Yucatan mini pigs that received either controlled cortical impact (CCI) or rotational acceleration injury (RAI). An additional goal in developing this cognitive battery was to activate limbic networks while animals are wirelessly recorded with high density laminar electrodes in the hippocampus (HC) and medial prefrontal cortex (mPFC). In the Delayed Match to Sample Sequence (DMTSS) task, pigs must learn to choose a random stimulus image out of four image choices. Subsequent phases include a random delay (0.5-6 seconds) between stimulus presentation and the response screen and a sequence of two image stimuli that the animal must remember to reproduce. Injured animals (CCI n=7) at the 0.5s delay across phases had a significant drop (p=0.004) in correct responses post-injury, however recovered quickly to baseline after 6.7 sessions. In the Image Reward Task (IRT), three stimulus images are each assigned a different number of reward pellets. Animals are presented with two stimuli per trial and must choose the image with the higher reward value. After reaching criteria (85% correct response) animals are presented with either an image reversal (three new stimuli) or a value reversal (the highest and lowest value stimuli swap reward values). Animals (n=3) were evaluated with categorical images (images of a tree, pig, and human) as well as abstract image stimuli (kaleidoscope fractal images). The injured animal took 7 sessions to recover to performance baseline post-CCI. In the delayed alternating T-maze, animals learn to alternate between right and left maze arms with a variable delay between trials (2-120s). Injured pigs (RAI n=2, CCI n=4) experienced a significant drop (p=0.038) in correct responses post-injury in 30s delayed trials, yet recovered quickly to baseline in an average of 3 sessions. In concurrent wireless electrode recordings, we identified HC neurons specific to spatial locations (place cells) as well as PFC neuronal ensembles organized around specific image pairs. This preliminary data suggests these fronto-hippocampal dependent tasks may detect deficits post-TBI in early periods while activating limbic circuitry. Ultimately, these cognitive tasks combined with simultaneous high-density recordings in these regions will help identify the electrophysiological basis for these deficits.

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Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.04/X12

Topic: D.04. Brain Injury and Trauma

Title: Genetic Background Influences the Detection of Behavioral Phenotypes Following Mild Traumatic Brain Injury

Authors: C. PICK[1], ***L. BIKOVSKI**[2];
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Abstract: Mild traumatic brain injury (mTBI) accounts for 80-90% of all traumatic brain injuries. However, only a subset of affected individuals develops persistent symptoms, and similar variability is observed in preclinical models. While injury severity and experimental design contribute to this heterogeneity, the role of genetic background remains unclear.To determine whether mouse strain influences behavioral outcomes following mTBI, we compared inbred C57BL/6 and outbred ICR mice. Adult males underwent closed-head weight-drop mTBI or sham procedures and were evaluated 7-14 days later using gait analysis (CatWalk XT), motor, affective-like, cognitive, and continuous home-cage behavioral assessments. A total of 112 mice were tested.Across conventional behavioral assays, most significant effects were attributable to strain rather than injury. Gait analysis revealed significant strain × injury interactions. Under baseline conditions, ICR mice displayed faster locomotion and a narrower hind paw base of support than C57 mice, but these differences were attenuated following mTBI. In addition, mTBI reduced running speed within the ICR strain.Home-cage monitoring revealed the strongest injury-related effects and marked strain dependence. Following mTBI, ICR mice showed reduced active-phase locomotion, diminished active-to-inactive phase differences in locomotion and shelter-related behaviors, and increased sustained shelter occupancy during the active phase. Comparable injury-related alterations were not detected in C57 mice. Habituation profiles also differed substantially between strains, with broader habituation observed in ICR mice.These findings indicate that behavioral consequences of mTBI are subtle and strongly influenced by genetic background. The detectability of mTBI-related phenotypes appears to depend on strain-specific behavioral characteristics and assay sensitivity. Outbred ICR mice may provide a more sensitive platform for detecting subtle behavioral alterations following mTBI, with important implications for model selection, reproducibility, and translational interpretation.

Disclosures: C. Pick: None. **L. Bikovski:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.05/X13

Topic: D.04. Brain Injury and Trauma

Support: VA Merit Award I01BX004625
VA Merit Award I01BX006372-01
VA Research Career Scientist Award IK6BX005647-01

Title: Transgenic mice with NHE1 deficiency in oligodendrocytes are resistant to chronic white matter degradation and mitochondrial damage following repetitive mild TBI

Authors: *A. C. WANG[1], H. OFT[2], M. REID[2], J. COLLIER[2], O. CAPUK[2], V. FIESLER[2], L. M. FOLEY[3], T. K. HITCHENS[6], G. KOHANBASH[4], Q. PADIATH[5], D. SUN[2];
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Abstract: Repetitive mild traumatic brain injuries (rmTBIs) are concussive events that can lead to chronic functional deficits with limited therapeutic options. While oxidative stress and mitochondrial dysfunction—hallmarks of rmTBI—are known to inhibit myelin and oligodendrocyte precursor cell (OPC) differentiation, whether rmTBI induces long-term vulnerability across the entire oligodendrocyte (OL) lineage remains to be determined. To study these mechanisms, a Pdgfra-creER$^{TM+/-}$;Nhe1$^{f/f}$ mouse model was developed to investigate the impact of an OL-specific conditional knockout (cKO) of the sodium-hydrogen ion exchanger NHE1, an oxidative stress regulator protein, on recovery from rmTBI-mediated brain injury. rmTBIs were induced with a controlled cortical impact device, with five total impacts of strike depth 1 mm given at 48-hour intervals. 50 days post-injury, sections from adult male and female mice (n = 4-6/group) were selected for histological immunostaining analysis to quantify changes to OL lineage cells in the corpus callosum (CC). Compared to Sham ctrl, Sham cKO, and rmTBI cKO cohorts, immunostaining results indicated that rmTBI ctrl brains displayed a significant reduction in total Olig2+ OL and mature OL counts (CC1+) ($p < 0.05$), with a concurrent increase in undifferentiated OPCs (NG2+) as well ($p < 0.05$). These changes were not observed in rmTBI cKO mice. To assess metabolic stress, markers of mitochondrial and oxidative damage were also quantified. The rmTBI ctrl mice exhibited elevated expression of oxidative stress markers PINK1 and NOX2 ($p < 0.05$), coupled with a significant downregulation of the mitochondrial protein cytochrome c oxidase (COX4) relative to Sham ctrl and cKO mice ($p < 0.05$). Together, these changes demonstrate that rmTBI disrupts OL mitochondrial function. However, rmTBI cKO mice showed preserved COX4 expression and low PINK1 and NOX2. In terms of white matter, rmTBI ctrl mice showed a marked loss in neurofilament light chain (NF-L) immunofluorescence intensity alongside an increase in degraded myelin basic protein (dMBP) ($p < 0.05$). This dual phenotype, reinforced by TEM analysis, indicates substantial axonal injury and myelin breakdown. Deletion of NHE1 limited this pathology, preserving white matter on ex vivo MRI DTI ($p < 0.05$). Collectively, these results demonstrate that rmTBI precipitates chronic mitochondrial dysfunction within oligodendrocytes and myelin loss. Deletion of NHE1 in OLs largely mitigated rmTBI impairment, highlighting these cells as a promising therapeutic target. These findings establish a framework for ongoing RNA-sequencing to determine mechanisms of oligodendrocyte pathology.

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Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.06/X14

Topic: D.04. Brain Injury and Trauma

Title: Efficacy of Visual Behavioral Tasks in Measuring Functional Deficits After Traumatic Brain Injury to Rat Visual Cortex

Authors: *N. SATISH, E. GAIESKI, A. LI, M. SJOHOLM, D. JGAMADZE, H.-C. I. CHEN; Dept. of Neurosurg., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Methods exist to characterize structural and functional damage to the visual cortex after injury, but there is no established behavioral assay to quantify loss of function after traumatic injury. This gap is relevant in the development of regenerative stem cell therapies, such as organoid transplantation, which aim to restore function.Eight-week-old male Long-Evans rats performed a random coherence dot-motion discrimination task. Dots moving left or right appeared on a touchscreen, with rats receiving a chocolate milk reward upon pressing the correct side. Each rat served as its own control, completing the task 5 times a week before and for 8 weeks after fluid percussion injury (FPI, n=3) or controlled cortical impact (CCI, n=4) to the primary visual cortex or sham injury control (n=3). Craniotomies were centered at 5 mm posterior and 2.5 mm lateral from bregma. CCIs were performed via cylindrical tipped impactor (diameter: 3 mm, penetration depth: 2 mm). FPIs were performed via luer lock connector (inner diameter: 2.2 mm, impact pressure: 2 atm)**.** Rats were perfused and immunohistochemistry was performed. Initial analysis did not reveal a consistent injury effect in the CCI and FPI groups compared to sham-injured controls. Logistic regression revealed response accuracy to be positively correlated with both coherence and reaction time (RT). Accuracy was also affected by stimulus sequencing effects, with the cohort performing significantly better on *same-side* trials (consecutive stimuli in same direction) than *opposite-side* trials (consecutive stimuli in opposite direction). Accuracy was graphed as a function of RT, split by coherence and stimulus sequence. On *opposite-side* trials, FPIs showed a possible performance deficit, with significantly lower accuracy and slower RTs. CCIs showed a similar deficit on slow RTs only. Both injury groups maintained baseline accuracy on *same-side* trials. Sham accuracy decreased on all trials with faster RTs.Our results suggest reduced discrimination ability in the injury groups and an altered task approach in the sham group. Conventional behavioral assays may lack sufficient sensitivity to characterize visual deficits in injury models. Invasive surgery carries the inherent risk of altering the rat's task engagement, making injury deficits difficult to distinguish from surgery-induced behavior changes. Future assays should minimize the moderation of task performance by behavioral state. For example, longer reward durations may reduce stimulus sequencing effects and registering responses on buttons peripheral to the stimulus display may increase the probability that data reflects the rat following the visual cue.

Disclosures: N. Satish: None. **E. Gaieski:** None. **A. Li:** None. **M. Sjoholm:** None. **D. Jgamadze:** None. **H.I. Chen:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.07/X15

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant EY032908-05
NIH Grant T32 EY013360
BrightFocus Foundation
Research to Prevent Blindness
Alcon Research Institute

Title: Characterizing the dorsolateral geniculate nucleus following monocular optic nerve crush

Authors: *M. AUM[1], S. MCCRACKEN[3], V. FAN[2], P. R. WILLIAMS[4];
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Abstract: The dorsolateral geniculate nucleus (dLGN) of the thalamus relays visual information from the retina to the visual cortex and is essential for conscious vision. In blinding diseases such as glaucoma, the human dLGN undergoes significant atrophy, characterized by reduced anatomical volume and decreases in thalamocortical cell quantity and soma size. While these changes have been well-studied in non-human primate and feline models, they remain poorly characterized in mice, thus hindering the development of a murine model of transneuronal degeneration in the dLGN. Here, we employed a monocular optic nerve crush to assess degeneration in the dLGN. At either three or six months post crush, cholera toxin-B (CTB) was injected into the vitreous body of the eye as an anterograde tracer to visualize the region. Using serial sectioning and subsequent volumetric reconstructions of the dLGN, the volume and density of neurons, microglia, and astrocytes in the dLGN ipsilateral and contralateral to the injury, as well as in eye-specific subregions within each dLGN were quantified to characterize transneuronal responses following injury. Monocular optic nerve crush resulted in a substantial reduction in volume of the dLGN receiving input from the crushed eye, with a continued, but smaller, decrease at six months. These changes were reflected in both neuronal and microglial populations, as neuronal cell numbers decreased within crushed-eye subregions while microglial cell numbers increased, producing corresponding shifts in density. These results establish a quantitative baseline for ongoing preservation studies aimed at reducing the severity of transneuronal degeneration following optic nerve injury.

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Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR053.08/X16

Topic: D.04. Brain Injury and Trauma

Support: Natural Sciences Fellows - High Point University
Undergraduate Research and Creative Works - High Point University

Title: Combat Athlete Weight Cutting Dehydration-Rehydration Reveals Increased Vulnerability to Mild Traumatic Brain Injury in Long-Evans Rats

Authors: *I. FRANKOVIC, A. SHUTTERS, H. CULBRETH, B. BIGLARI, W. R. KOCHEN; Neurosci., High Point Univ., High Point, NC

Abstract: Combat athletes face a heightened risk of mild traumatic brain injury (mTBI) due to the inherent physical contact with their sport. These athletes also frequently undergo extreme weight-cutting practices, often involving significant dehydration, to meet competition weight classes. Despite rehydration before competition, it remains unknown whether the prior dehydration period leaves the brain more vulnerable to injury. To model combat weight cycling, we investigated whether dehydration followed by rehydration exacerbates behavioral and neuroinflammatory outcomes after mTBI in a rat model. Seventy Long Evans rats (35 female; 35 male; 150 - 250 g) were randomly assigned to control, mTBI, dehydration, or dehydration + mTBI groups. mTBI was induced using a modified Kane weight drop model (200 g, 18 in). Dehydration consisted of a 48 hour water restriction (6-10% body weight loss), followed by a 24 hour rehydration period. We recorded rat body weight at baseline, post-dehydration, and post-rehydration. Behavioral outcomes were assessed using the open field test, novel object recognition test, and elevated zero maze. Fecal boli was recorded as an additional measure of stress-related behavior and behavior was analyzed using BehaviorCloud automated tracking software. Dehydrated rats exhibited significant weight loss followed by recovery to near baseline body weight after rehydration ($p < 0.001$), confirming a successful model of rapid weight cycling. Histological examination of acute post-injury brain tissue samples revealed no structural abnormalities across groups, validating the mildness model of the concussion. Open field analysis demonstrated a significant dehydration x mTBI interaction for the time spent in the center ($F(1,33)=4.553$, $p = 0.040$), with dehydrated rats exhibiting reduced center exploration consistent with increased anxiety-like behavior. Novel object recognition analysis revealed a significant three-way interaction between dehydration, mTBI, and sex interaction for fecal boli production ($F(1,33)=4.789$, $p=0.036$). Male rats in the dehydration + mTBI group produced more fecal boli than sham males ($p=0.018$), hydrated males ($p=0.048$), and dehydration + mTBI females ($p=0.035$), suggesting enhanced stress reactivity in males exposed to dehydration and mTBI. These preliminary findings indicate that dehydration prior to mTBI may worsen its symptomatic behavioral outcomes despite subsequent rehydration, with potential sex-specific

effects. Ongoing analysis will further characterize the symptomatic and neuroinflammatory consequences of pre-injury dehydration and their implications for combat athletes.

Disclosures: I. Frankovic: None. **A. Shutters:** None. **H. Culbreth:** None. **B. Biglari:** None. **W.R. Kochen:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.09/X17

Topic: D.04. Brain Injury and Trauma

Support: NIH P20GM103449

Title: Exploring Mitochondrial Function and Integrity Following Repeated Closed Head Trauma

Authors: *E. PATE[1], Y. MOUSA[1], G. CLEMENTE[1], S. ZHANG[1], M. MORRIS[1], L. ZATE[1], A. CROCKER[2];
[2]Neurosci. Program, [1]Middlebury Col., Middlebury, VT

Abstract: Traumatic brain injury (TBI) is a leading cause of neurological morbidity worldwide, yet the cellular and molecular mechanisms driving progressive secondary injury are not fully understood. There is a critical gap between how distinct glial signaling programs interact with mitochondrial quality control pathways, and how these determine whether neural tissue recovers from trauma or progresses toward neurodegeneration. Here, we use *Drosophila melanogaster* as a genetically tractable model of closed head trauma (CHT). Using this model, we further investigate mitochondrial integrity, electron transport chain (ETC) functionality and reactive oxygen species (ROS) generation of single and repeated injury, and how these signaling programs relate to glial versus neuron mitochondrial integrity. Using a piezoelectric CHT device to deliver graded, reproducible compression, combined with transgenic fluorescent reporters and ETC/ROS assay measurements we hypothesize that repeated injury will show progressive loss of mitochondrial integrity and increased cellular stress. Our results show reduced ATP5a (protein critical to the catalytic core of the mitochondrial ATP synthase - Complex V) following repeated injury, independent of severity of CHT. This points towards a reduction in mitochondrial integrity and ETC functioning. Preliminary data suggests that both MitoTimer (reporter for ROS) and MitoQC (mitophagy reporter) show increased activity post CHT. This increase is seen in both glial cells and neurons, and is more prominent in neurons. Preliminary data also suggests that the NAD+/NADH ratio is reduced following repeated injury, and is even lower for single injury. The NAD+/NADH ratio is a direct indicator of cellular redox state and mitochondrial energy metabolism. A higher ratio reflects greater oxidative activity, while a lower ratio suggests impaired oxidative phosphorylation. Total NAD levels varied greatly between the groups, where those with repeated concussion were lower than those with single concussion. This suggests single concussions have increased total NAD formation, but decreased NAD+ formation. We

also found that there is a progressive increase in Cytochrome C oxidation across the control, single, and repeated injury. This points to potential decoupling of the ETC following repeated injury. The Drosophila CHT platform established here will allow us to pursue mechanistic investigations into energy failures following repeated injury that we see across species. This work can also be the foundation of identifying potential biomarkers for outcomes following repeated injury.

Disclosures: E. Pate: None. **Y. Mousa:** None. **G. Clemente:** None. **S. Zhang:** None. **M. Morris:** None. **L. Zate:** None. **A. Crocker:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.10/X18

Topic: D.04. Brain Injury and Trauma

Title: Traumatic Brain Injury and Ethanol Impair Climbing Performance in Drosophila melanogaster

Authors: *J. VASU[1], R. E. HARTMAN[2];
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Abstract: Traumatic brain injury (TBI) frequently co-occurs with alcohol use, and clinical research suggests ethanol exposure worsens post-TBI motor ability. Path tortuosity, or meandering, is a marker of motor impairment in humans with TBI or under the influence of alcohol. Drosophila melanogaster provide a high throughput model of TBI and ethanol exposure, but conventional cohort-level climbing assays do not reveal individual differences in climbing path quality. We adapted FreeClimber, open-source automated animal tracking for Drosophila climbing analysis, to support per-fly trajectory linking and analysis for meandering. The extended software (FreeClimber-FNG) uses TrackPy velocity-predictive linking to maintain individual fly identities across frames and computes per-bout path-quality metrics including tortuosity and turning radius. Adult Drosophila melanogaster (N = 240) were assigned to: Sham, TBI, EtOH, or TBI+EtOH conditions. Flies in the experimental groups were given TBI with a high impact trauma device (HIT), exposed to vaporized EtOH for 10 minutes, or both. TBI and EtOH each elevated tortuosity relative to sham (TBI $p<.0001$; EtOH $p=.0002$), and the combined condition produced greater impairment than either insult alone (vs. TBI $p=021$; vs. EtOH $p < .0001$). These findings (1) demonstrate that per-fly path-quality metrics capture motor information not detectable in cohort-averaged climbing readouts and (2) that TBI and ethanol produce additive meandering behavior in Drosophila melanogaster.

Disclosures: J. Vasu: None. **R.E. Hartman:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.11/X19

Topic: D.04. Brain Injury and Trauma

Support: NIH grant R01NS133233

Title: Traumatic Brain Injury Induces PAD4-Mediated NET Formation and Neurovascular Dysfunction

Authors: *T. BARRIOS LIZON[1], S. CHAVAN[1], P. A. MUNEER[2];
[2]Biomed. Engin., [1]Florida Intl. Univ., Miami, FL

Abstract: Traumatic brain injury (TBI) induces rapid neurovascular disruption and innate immune activation, but the mechanisms linking peripheral neutrophil responses to secondary vascular injury remain incompletely defined. Neutrophils are among the earliest immune cells recruited after TBI and can undergo neutrophil extracellular trap formation, releasing decondensed chromatin decorated with granular proteins into the injured microenvironment. Although NETs are increasingly recognized as mediators of inflammation and thrombosis, their mechanistic relationship to post-traumatic microvascular pathology remains unclear. We hypothesize that TBI promotes PAD4-dependent NET formation within the injured brain and cerebral microvasculature, contributing to endothelial dysfunction, intravascular thrombosis, and impaired neurovascular remodeling. To define this mechanism, we examined changes in NET-associated markers following experimental TBI, with emphasis on peptidyl arginine deiminase 4 (PAD4), citrullinated histone H3 (H3Cit), myeloperoxidase (MPO), and neutrophil accumulation. Immunofluorescence based analyses were used to assess NET marker expression in relation to microvascular structures, while molecular assays were used to evaluate injury-induced changes in PAD4-associated pathways. In parallel, endothelial-neutrophil interaction assays were used to investigate whether brain endothelial injury promotes neutrophil activation and NET-associated responses. Our findings support a model in which TBI triggers neutrophil recruitment and PAD4-associated chromatin decondensation, resulting in NET accumulation near injured cerebral microvessels. NET-associated markers localize with vascular compartments, suggesting a mechanistic link between neutrophil activation, endothelial injury, and thromboinflammatory microvascular dysfunction after TBI. Together, these studies identify PAD4-dependent NET formation as a key neuroimmune mechanism contributing to secondary neurovascular injury and provide a framework for understanding how innate immune responses shape vascular pathology after brain trauma. This work was supported by the NIH grant R01NS133233 to P. M. Abdul Muneer.

Disclosures: T. Barrios Lizon: None. **S. Chavan:** None. **P.A. Muneer:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.12/X20

Topic: D.04. Brain Injury and Trauma

Support: NIH NINDS Grants CDM K01NS121195
MLH K00NS125825

Title: TRPV4 Participates in Headache Induction Following Mild TBI with Involvement of Astrocytes

Authors: *R. CHUNDURI[1], M. L. HERNANDEZ[2], C. MOORE[2], M. FOUANI[2];
[2]Neurol., [1]Duke Univ., Durham, NC

Abstract: Post-traumatic headache (PTH) is a common consequence of mild traumatic brain injury (mTBI) that often presents migraine-like symptoms, yet its cellular and molecular mechanisms remain poorly understood. Transient Receptor Potential Vanilloid 4 (TRPV4), a calcium-permeable non-selective cation channel, is broadly expressed throughout the nervous system and has been implicated in mechanotransduction, nociceptive signaling, and headache. We hypothesize that TRPV4 contributes to the development and persistence of PTH following mTBI. To investigate the role of TRPV4 in PTH, we used both global TRPV4 knockout (KO) mice (n=52) and astrocyte-specific conditional-tamoxifen inducible TRPV4 KO (Aldh1L1Cre-TRPV4lox/lox, n=28) mice (12- 20 weeks) in a closed head injury model in adult male and female mice. The studies were also randomly assigned coded identifiers to support blinded behavioral assessment, as well as 2 cohorts for astrocytic TRPV4 KO and 4 cohorts for global TRPV4 KO. Behavioral testing was performed every other day for 2 weeks after mTBI to assess periorbital mechanical hyperalgesia using the Von Frey test, allodynia (using repetitive VF), and motor coordination using the rotarod test. Global TRPV4 KO mice exhibited reduced pain-related behavior following closed-head injury compared with wild-type controls, supporting a role for TRPV4 in PTH-like pain after mTBI. Compared with injured control mice, tamoxifen-treated Aldh1L1Cre-TRPV4lox/lox mTBI mice, using a mixed effects model, presented significantly reduced hyperalgesia beginning on day 7 (Tukey's post hoc test, p=.0046) and reduced allodynia beginning on day 3 (Tukey's post hoc test, p=.0002) compared to their oil-treated counterparts. Rotarod assays further suggested that astrocytic TRPV4 deletion may influence motor outcomes, as tamoxifen-treated mTBI mice spent less time on the rotarod, indicating reduced motor coordination. Fluorescence imaging was also performed with GFAP, CD-31, and TRPV4 markers to further support these findings and to confirm TRPV4 KO in the mice. Overall, these findings indicate TRPV4 involvement in post-traumatic head pain, with cell-specific contributions from astrocytic TRPV4. This work identifies TRPV4 as a promising molecular target for future study and highlights the need to further evaluate its role in PTH.

Disclosures: R. Chunduri: None. **M.L. Hernandez:** None. **C. Moore:** None. **M. Fouani:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

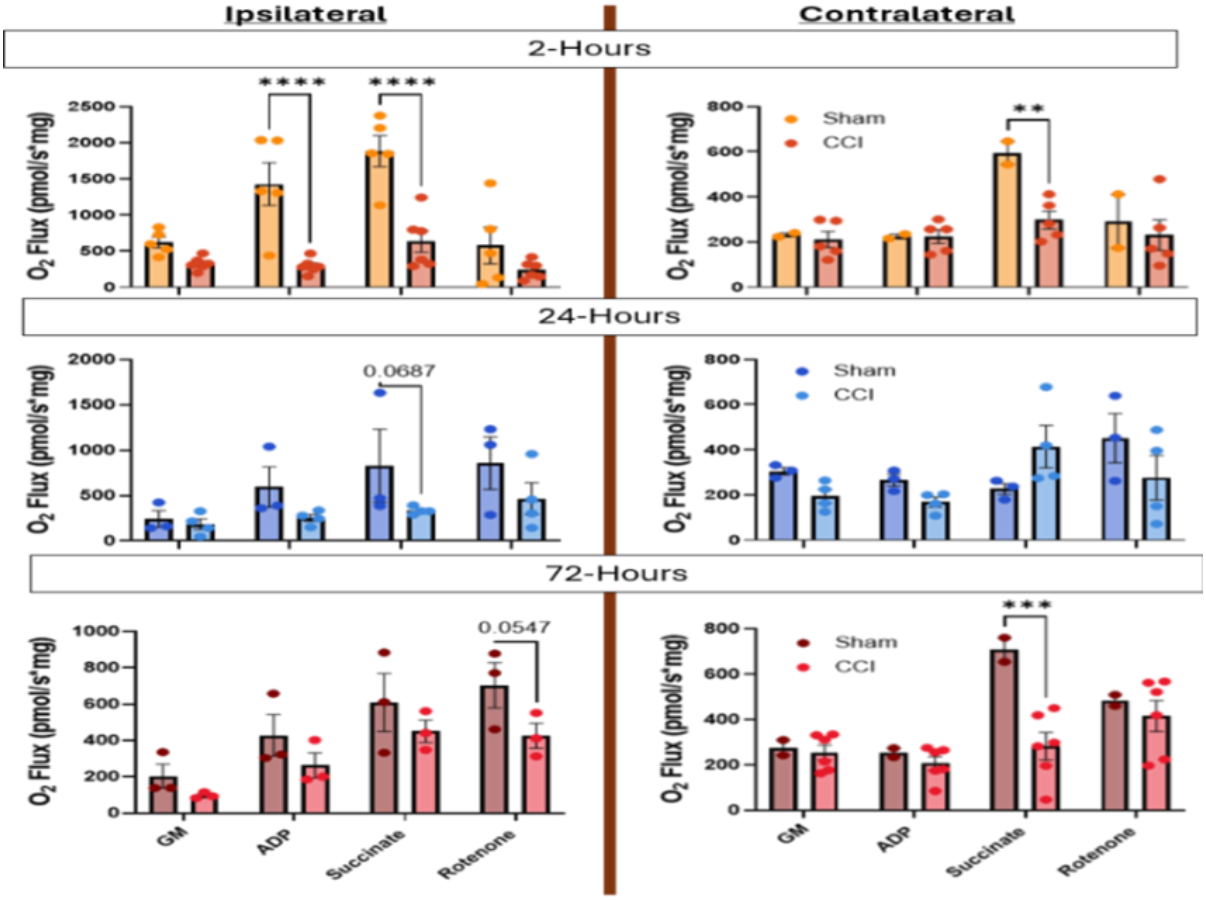
Program #/Poster #: PSTR053.13/X21

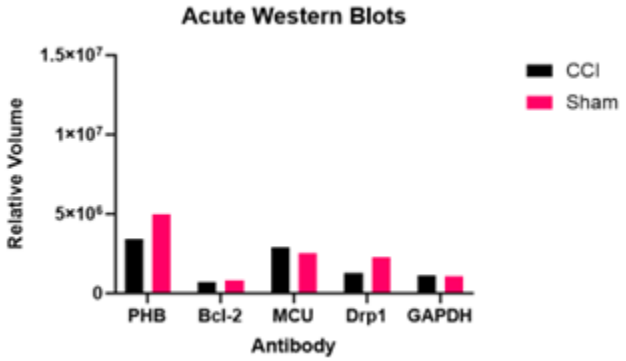
Topic: D.04. Brain Injury and Trauma

Title: Mitochondrial function is dysregulated after a traumatic brain injury

Authors: *C. MCNEAL[1], R. DESAI[2], S. DANTULURI[2], C. FRASIER[3];
[1]East Tennessee State Univ., Johnson City, TN; [2]East Tennessee State Univ., Knoxville, TN, ;
[3]East Tennessee State Univ., Johnson City, TN.

Abstract: Traumatic brain injuries (TBI), which is defined as a violent blow to the head, can result in seizure activity. While mechanisms of neuronal injury in TBI and seizures are well studied, the progression of post-traumatic epilepsy (PTE) is understudied. We hypothesize that by uncovering the progression of energetics during the progression from TBI to PTE, we can find potential markers that are indicative of increased PTE risk. Our lab uses a controlled cortical impact mouse model and video-EEG-ECG to investigate the progression of seizures and investigate mitochondrial function at defined timepoints (2-, 24-, and 72- hours) to study mitochondria's role in seizure pathology. Mitochondria were isolated from both hippocampal and cortical regions from both the ipsa- and contralateral hemispheres. So far, our lab has seen evidence of an increase in Complex-II-driven respiration across acute timepoints. We've also found a significant decrease in ATP production 2 hours post-injury on the ipsilateral side. Also ipsilaterally, Complex-I is shown to be dysregulated 72 hours post-injury. To investigate cell death pathways and the structural integrity of mitochondria, we utilized western blots of various proteins. A noticeable decrease in PHB and Drp1 indicate that the structure of the mitochondria has been disrupted post-injury and that mitophagy processes are being affected as well. Overall, PTE appears to have multiple sites of dysregulation within the mitochondria at various timepoints.





Disclosures: C. McNeal: None. **R. Desai:** None. **S. Dantuluri:** None. **C. Frasier:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.14/X22

Topic: D.04. Brain Injury and Trauma

Support: COBRE P30 GM149367
NIMHD U54 MD007600
S21MD001830
Title V P031S200104 P031S160068

Title: Characterization of NLRP3 Inflammasome Activation Along the Gut-Brain Axis Following Traumatic Brain Injury

Authors: *P. VÁQUEZ MARTÍNEZ;
Univ. of Puerto Rico, Med. Sci. Campus, Cayey, Puerto Rico

Abstract: Concussive brain injury activates the NLRP3 inflammasome, a multiprotein complex that drives neuroinflammation in response to injury. This complex activates caspase-1, which cleaves pro-IL-1β and pro-IL-18 into their mature forms. Although it is well known that neuroinflammation can cause neurological dysfunction, the role of these cytokines during the chronic phase after injury is unclear. To address this issue, we modeled concussion using a weight-drop model of repeat closed head injury (rCHI) (three impacts delivered over one week) in adult male rats. Then we assessed behavioral and inflammatory outcomes. At 1 day post-injury, the open field test was used to assess exploratory behaviors, such as distance traveled and time spent in the periphery. Distance traveled was identical between groups (rCHI: 23.91 m, Sham: 26.12 m, $p = 0.27$, $t_{24}=1.13$), suggesting that rCHI does not affect locomotion. However, we observed an increased time in the periphery in rCHI rats compared to sham rCHI: 269.89 s, Sham: 244.6 s, $p = 0.047$, $t_{24}=2.10$), suggesting increased anxiety-like behavior. Preliminary data from a separate cohort, assessed at 49 days post-injury, showed that a decrease in TNF-α ($p = 0.030$, $t_4 = 3.31$) and caspase-1 ($p = 0.011$, $t_6 = 3.63$) levels compared to sham in serum. These results suggest that inflammation may be compartmentalized to the brain rather than systemic. Furthermore, these pro-inflammatory cytokines may disrupt intestinal tight junctions, increasing gut permeability and allowing microbial metabolites to enter the circulation. This translocation could amplify both systemic and neuroinflammation, creating a self-sustaining inflammatory loop that exacerbates neurological deficits.

Disclosures: P. Váquez Martínez: None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.15/X23

Topic: D.04. Brain Injury and Trauma

Support: R37NS133195

Title: Investigating Human Schwann Cell-derived Exosome Treatment on Modulating Secondary Injury and Enhancing Reparative Mechanisms After Traumatic Brain Injury in Mice

Authors: *I. AKPU[1], M. BLAYA[2], J. SANCHEZ-MOLANO[3], Y. PRESMAN[4], H. M. BRAMLETT[5], W. DIETRICH[2];
[1]Neurosurg., Univ. of Miami, Coral Gables, FL; [2]Neurosurg., Univ. of Miami, Miami, FL; [3]Neurosurg., Univ. of Miami, Miramar, FL; [4]Univ. of Miami, miami, FL; [5]The Univ. of Miami Dept of Psychology-Neuroscience Major, Miami, FL.

Abstract: Traumatic brain injury (TBI) initiates a complex spectrum of pathophysiological and debilitating behavioral consequences that profoundly diminish the quality of life for patients, their families, and the healthcare system. Despite decades of preclinical advancement, the successful translation of neuroprotective interventions into a multicenter clinical setting remains an elusive goal. This persistent translational gap underscores the urgent need for novel therapeutic strategies that can effectively navigate the brain's physiological barriers to improve long-term neurological outcomes. Exosomes, a specialized class of extracellular vesicles (EVs), have emerged as promising therapeutic for neurodegenerative disorders due to their capacity to traverse the blood-brain barrier and deliver bioactive cargo, including miRNAs, proteins, and lipids that modulate recipient cell function. Recent studies for our laboratory have demonstrated the therapeutic potential of Human Schwann cell-derived exosomes (hSC-Exos) in a penetrating ballistic brain injury (PBBI) rat model and a fluid percussion injury (FPI) rat model, where they significantly attenuated neuroinflammation, programmed cell death, and glial activation. My project aims to investigate hSC-Exos administration in a murine controlled cortical impact (CCI) model to elucidate their role in modulating secondary injury while simultaneously augmenting endogenous reparative processes to enhance neurorepair. Overall, I hypothesize that intravenous administration of hSC-Exos after TBI will target multiple secondary injury mechanisms as well as reparative processes leading to improved histopathological and long-term behavioral outcomes. Results demonstrated that the administration of hSC-Exos intravenously, 30 minutes after CCI induction significantly reduced the expression of inflammasome proteins such as Casapse-1, ASC and Interlukin-18 (IL-18) in the cerebral cortex and hippocampus. miRNA profiling was performed across experimental groups (Sham + Vehicle, CCI + Vehicle, and CCI + hSC-Exos) to identify differentially expressed miRNAs and quantify the magnitude of their modulation following injury and treatment. Results revealed an upregulation in several anti-inflammatory miRNAs such as miR-451a, miR-182-5p and miR-486-5p suggesting the hSC-Exos modulation on these bioactive molecules. Collectively, these data demonstrate that hSC-Exos may serve as a potent therapeutic for TBI by attenuating secondary injury cascades and facilitating the translation of regenerative therapies from bench to bedside.

Disclosures: I. Akpu: None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.16/X24

Topic: D.04. Brain Injury and Trauma

Support: VA (I01BX006062)
NIH (R35NS132184)

Title: Ascorbate-mediated modulation of DNA hydroxymethylation promotes post-TBI neuroprotection

Authors: *P. JOSHI, C. KOZHIKKADAN DAVIS, R. VEMUGANTI;
Neurolog. Surgery, Univ. of Wisconsin-Madison, Madison, WI

Abstract: Epigenetic modifications such as DNA methylation (5mC; 5-methylcytosine) and hydroxymethylation (5hmC; 5-hydroxymethylcytosine) are increasingly being recognized as therapeutic targets for CNS disorders. Many studies have shown that TBI can induce changes in 5mC patterns, especially in genes associated with neurodegenerative disorders. However, the role of 5hmC (oxidized form of 5mC), which is known to enhance transcription of protective genes and promote neuronal survival under adverse conditions, remains to be explored after TBI. We currently evaluated the genomic 5hmC status using hMeDIP-seq following TBI in adult C57BL/6 mice of both sexes subjected to mild to moderate controlled cortical impact (CCI) injury. In the peri-lesional cerebral cortex, TBI significantly induced TET activity at 12h after injury, and several genomic loci showed differential hydroxymethylation at 6h, 24h, and 72h after injury compared to sham. Immunostaining showed that increased 5hmC levels after TBI were mainly located in the neurons. Since ascorbate (Vitamin C) is a cofactor to the Ten Eleven Translocation (TET) proteins that mediate the conversion of 5mC to 5hmC, we tested whether increasing the levels of 5hmC with ascorbate treatment improved post-TBI functional outcomes. Treatment with ascorbate (500 mg/Kg to 1,000 mg/Kg; at 5 min, 24h, and 48h after injury) significantly induced TET activity and 5hmC levels in the peri-lesional cortex at 72h after TBI. The ascorbate-treated cohort also showed improved motor function recovery (rotarod test and beam walk test) and reduced lesion volume following TBI compared with the vehicle-treated cohort. Furthermore, the differentially hydroxymethylated genes in the ascorbate/TBI cohort compared to the vehicle/TBI cohort were associated with inflammatory and stress pathways. Thus, our studies show that ascorbate treatment can modulate the levels of the 5hmC epigenetic modification and can result in enhanced neuroprotection after TBI. Funded by the US VA and NIH.

Disclosures: P. Joshi: None. **C. Kozhikkadan Davis:** None. **R. Vemuganti:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.17/X25

Topic: D.04. Brain Injury and Trauma

Title: Effects of Prophylactic Creatine Supplementation on Mild Traumatic Brain Injury in Long-Evans Rats

Authors: *H. CULBRETH, I. FRANKOVIC, A. SHUTTERS, B. BIGLARI, W. R. KOCHEN; Neurosci., High Point Univ., High Point, NC

Abstract: Creatine supplementation enhances athletic performance by promoting cellular energy production and muscle growth. Although its potential neuroprotective effects have been explored, the impact of creatine on outcomes following traumatic brain injury (TBI) remains incompletely understood. This study investigated whether pre-injury creatine supplementation provided neuroprotective effects following mild traumatic brain injury (mTBI) in Long-Evans rats. Seventy Long-Evans rats (34 female, 36 male) were assigned to one of four groups: control, creatine, mTBI, or creatine + mTBI. Creatine-treated rats received a three-week supplementation regimen consisting of a one-week loading dose equivalent to 20 g/day in humans followed by maintenance doses equivalent to 5 g/day. Rats in mTBI groups received injury via a 200-g weight drop from 18 inches. Following injury, four rats per group were immediately euthanized for acute analyses. Remaining animals completed behavioral testing, including open field, novel object recognition, and elevated zero maze assessments. Following testing, tissues were collected for biochemical analyses. Preliminary findings indicate significant interactions among sex, mTBI, and creatine treatment on behavioral outcomes ($p < 0.05$). Creatine + mTBI rats demonstrated shorter righting times than other groups ($F(1,62) = 5.261$, $p = 0.025$), suggesting improved acute recovery. However, these animals spent less time in the center of the open field ($F(1,44) = 5.178$, $p = 0.028$). Novel object testing revealed a significant three-way interaction ($F(1,39) = 7.413$, $p = 0.010$), with unsupplemented TBI females exhibiting elevated fecal boli compared to males ($p = 0.01$) and creatine-treated females ($p = 0.02$). ELISA analyses demonstrated lower neurofilament light protein levels in creatine + mTBI rats relative to unsupplemented counterparts, indicating reduced neuroaxonal injury and neuroinflammation. Data analysis is ongoing, with additional behavioral video recordings currently being reviewed and scored. These findings suggest that pre-injury creatine supplementation modulates behavioral and biochemical responses following mTBI. Creatine-treated animals demonstrated improved acute recovery and reduced post-injury neurofilament light levels, supporting creatine as a potential preventative strategy for reducing injury burden and improving recovery following mild traumatic brain injury.

Disclosures: H. Culbreth: None. **I. Frankovic:** None. **A. Shutters:** None. **B. Biglari:** None. **W.R. Kochen:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.18/X26

Topic: D.04. Brain Injury and Trauma

Support: MTBI2
HPAPG7012224

Title: Assessing Adrenergic Dependent Roles of Microglia in Functional Glymphatic Recovery Following Traumatic Brain Injury

Authors: M. MITCHELL[1], *C. M. BOUSLOG[3], X. XU[4], F. W. LISCHKA[5], V. TSYTSAREV[2], C. A. BROWNE[6], D. L. DICKSTEIN[7], Z. GALDZICKI[8];
[2]APG, [1]Uniformed Services Univ., Bethesda, MD; [3]Uniformed Services Univ. of the Hlth. Sci., Silver Spring, MD; [4]Uniformed Services Univ. of the Hlth. Sci., Germantown, MD; [5]Anatomy, Physiol. and Genet., Henry M. Jackson Fndn. for the Advancement of Military, Bethesda, MD; [6]Biol. Sci., Munster Technological Univ., Cork, Ireland; [7]Pathology, Uniformed Services Univ. of Hlth. Sci., Bethesda, MD; [8]USU, Dept. of Anat, Physiol & Genetics, Sch. of Medicine, USU, Bethesda, MD

Abstract: Traumatic brain injury (TBI) can result in progressive cognitive decline and motor instability long after the initial injury. Although the exact mechanism that drives cognitive decline is still unknown, emerging evidence implicates glymphatic system dysfunction. The glymphatic system facilitates the clearance of metabolic waste through a perivascular network, driven primarily by the pulsatility of penetrating arteries. Arterial pulsatility is decreased post-injury following surges in the neurohormone noradrenaline, leading to impaired glymphatic clearance. While injury-induced “adrenergic storms” are known to impair clearance, the role of microglia (the brain’s resident immune cell) in modulating the adrenergic-vasculature interface remains largely unexplored. To evaluate the impact of microglia on glymphatic clearance, C57BL6/J mice were placed on a 3-week PLX 5622 or control diet to deplete CSF1R-sensitive microglia. Mice then received a moderate-to-severe controlled-cortical impact (CCI). A pan-adrenergic inhibition cocktail (propranolol, prazosin, and atipamezole) was administered 30 minutes, 1 day, and 2 days post-injury. Vasculature pulsatility was quantified 7 days post-TBI via in-vivo 2-photon imaging. Microglial morphology and 3D microglia-vasculature interactions were analyzed in transgenic CX3CR1-GFP+ mice. Moderate TBI (CCI=1.5mm) induces a reduction in the pulsatility of penetrating arteries, however this effect is not seen in microglia depleted mice with TBI. This mechanical deficit in the glymphatic “pump” was associated with motor impairment in microglia-intact groups, showing a modest effect size toward increased slips on the beam walk assay. Analysis is ongoing to determine if adrenergic inhibition affects the morphology of microglia and their subsequent proximity to perivascular spaces. These results so far suggest that microglia are essential for maintaining the homeostasis of norepinephrine signaling regulated vascular dynamics. Investigating the role microglia has in vasculature remodeling and regulation, offers a potential therapeutic target to mitigate glymphatic stagnation and improve neurocognitive outcomes following TBI.

Disclosures: M. Mitchell: None. **C.M. Bouslog:** None. **X. Xu:** None. **F.W. Lischka:** None. **V. Tsytsarev:** None. **C.A. Browne:** None. **D.L. Dickstein:** None. **Z. Galdzicki:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.19/X27

Topic: D.04. Brain Injury and Trauma

Support: College of Arts and Sciences, Quinnipiac University

Title: Dose-Dependent Effects of Mechanical Traumatic Brain Injury on Survival and Apoptotic Signaling in Adult Drosophila melanogaster

Authors: J. LALVAY[1], S. AZERRAD[2], *A. J. BETZ[3];
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Abstract: Traumatic brain injury (TBI) is a major cause of neurological dysfunction and is associated with the activation of apoptotic and neurodegenerative pathways. While mammalian models can be used for TBI, simpler systems such as *Drosophila* melanogaster provide a genetically tractable model for investigating conserved molecular responses to injury. In the present study, we utilized two mechanical models of traumatic brain injury (TBI) in *Drosophila melanogaster*: a spring-based impact model using a HIT-style apparatus ("bang" model) and a vortex-induced injury model to investigate survival and apoptotic signaling. Injury severity was manipulated by varying exposure to mechanical trauma, and survival was assessed 24 h post-injury. Following TBI induction, flies ' heads were collected 24 or 1 hours post-injury to assess molecular changes associated with apoptosis. Both injury paradigms produced dose-dependent reductions in survival, with severe injury conditions resulting in complete mortality. Sex differences emerged in vulnerability to the moderate "bang" condition. To assess apoptotic signaling, heads from surviving flies were collected 1 h and 24 h after injury and analyzed for cleaved Death caspase-1 (Dcp-1), Atg4 and DiCER expression by Western blot. Dcp-1 levels decreased with increasing injury severity, with flies exposed to two impacts exhibiting approximately 50% lower Dcp-1 expression than controls. These findings suggest that apoptotic signaling in surviving flies may differ from the acute injury response and highlight the importance of examining multiple post-injury time points. Further, sex differences emerged in survival and Dcp-1 levels and Dicer expression. Findings indicate that *dunc* mutants with disrupted cAMP signaling and partial *Tau* knockouts display greater susceptibility to mechanical injury than wild-type flies, with reduced survival observed following increasing injury severity. Ongoing studies will examine earlier time points and additional apoptotic markers to determine whether injury-induced cell death is transient or mediated by alternative caspase pathways.

Disclosures: J. Lalvay: None. **S. Azerrad:** None. **A.J. Betz:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.20/X28

Topic: D.04. Brain Injury and Trauma

Support: DoD ERP IDA W81XWH-22-1-0287
VA SPiRE IDA RX004629-01A1
VA MERIT I01RX003498
VA VISN 4 FY26 CCDF

Title: A translational swine platform to define sleep and circadian biomarkers of post-traumatic epilepsy after traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is associated with chronic sleep-wake disruption, cognitive impairment, and an increased risk of post-traumatic epilepsy (PTE). However, the sleep and circadian mechanisms linking brain injury to long-term neurological morbidity remain poorly characterized. Most preclinical studies of sleep and epileptogenesis rely on rodent models, limiting translation given differences in brain size and anatomy, sleep architecture and circadian phenotypes, and approaches to chronic intracranial monitoring. We are developing a translational swine platform to identify sleep-wake and circadian biomarkers of PTE after experimental TBI. Yucatan miniature pigs underwent controlled cortical impact (CCI) injury or sham procedures, followed by months of synchronized chronic intracranial video-EEG monitoring post-TBI. Long-duration recordings were paired with neurological assessment using the Pig Neuroscore and with cognitive/behavioral paradigms engaging prefrontal-hippocampal circuits. To enable scalable analysis of large-animal recordings, we implemented an artifact-aware sleep-scoring workflow with automated classification of wake, non-rapid eye movement sleep, and rapid eye movement sleep which was verified by blinded manual review. Sleep-architecture outcomes include total sleep time and efficiency, wake after sleep onset, non-REM and REM sleep duration, bout structure, fragmentation, and sleep-state transition probability. Ongoing analyses will relate these measures to neurological recovery, cognitive performance, and epileptiform EEG features. Preliminary analyses demonstrate the feasibility of chronic sleep-state classification in freely behaving pigs, despite large-animal movement artifacts and complex state transitions. TBI animals show evidence of persistent sleep-wake instability, including altered sleep continuity and fragmentation during chronic recovery. These abnormalities are being evaluated as candidate biomarkers of injury severity, cognitive outcome, and PTE vulnerability. This work establishes a large-animal framework for studying sleep and circadian disruption after TBI, using continuous intracranial video-EEG, behavioral phenotyping, and scalable sleep-state analysis. By integrating sleep architecture, circadian timing, cognition, and epileptiform activity in a clinically relevant swine model, this platform provides a foundation for future biomarker discovery and for testing sleep- and circadian-targeted interventions to improve post-TBI outcomes.

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

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.21/X29

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01NS128104
NIH Grant R21NS16611

Title: Neural Correlates of Motion: Deploying a Custom Markerless Pose Estimation Framework for High Resolution Locomotion Analysis in a Gyrencephalic Swine Model of Neurological Injury

Authors: *M. B. PATRICK, P. GOSWAMEE, A. D. LAFRENAYE;
Neurosci. and Anat., Virginia Commonwealth Univ., Richmond, VA

Abstract: Objective quantification of locomotor behavior remains a major challenge in translational neuroscience, particularly in large-animal models that more closely recapitulate human neuroanatomy and movement dynamics. Conventional behavioral scoring methods are inherently subjective, temporally and spatially limited, and insufficient for detecting subtle neuromotor deficits following traumatic brain injury (TBI). Despite the growing use of Yucatan minipigs in translational neurotrauma research, scalable markerless approaches for quantifying post-injury locomotor behavior in this model remain limited. To address these limitations, we developed and validated a top-down DeepLabCut (DLC) workflow for Yucatan minipig whole-body locomotor tracking which extracts injury-relevant movement features that are difficult to score manually. Overhead video recordings were used to extract whole-body movement trajectories, rather than limb-level gait kinematics, making it suitable for overhead recording in which limb visibility is limited. This approach enabled quantification of spatiotemporal locomotor features including velocity, directional changes, path structure, movement periodicity, and activity dynamics. Framework validity was assessed against spatial occupancy data scored by a blinded investigator across four experimental groups: sham-injured female, sham-injured male, mild traumatic brain injury (mTBI) female, and mTBI male. Mild TBI was induced using the central fluid percussion (cFPI) model, a well-established paradigm that delivers a controlled, bilateral pressure wave to the intact dura, producing a reproducible, diffuse brain injury with translational relevance to human concussion. This approach enables objective and scalable characterization of locomotor impairment following neurological injury without requiring limb visibility or manual scoring. The proposed framework demonstrates robust performance across experimental conditions and provides consistent extraction and assessment of movement-based behavioral metrics in a large animal neurotrauma model of neurological dysfunction, establishing a foundation for automated behavioral phenotyping in swine models and supporting the development of computational neurotrauma biomarkers for translational applications.
Keywords: DeepLabCut; pose estimation; locomotion analysis; Yucatan minipig; swine model;

traumatic brain injury; central fluid percussion injury; translational neuroscience; neuromotor biomarkers

Disclosures: M.B. Patrick: None. **P. Goswamee:** None. **A.D. Lafrenaye:** None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.22/X30

Topic: D.04. Brain Injury and Trauma

Title: Evaluating the proteomic and behavioral effects of an elastin-like polypeptide-delivered NF-kB inhibitor in traumatic injury

Authors: *J. HASKELL[1], B. E. GRAYSON[2], G. BIDWELL[1];
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Abstract: Traumatic brain injury (TBI) affects over 69 million people annually. TBIs consist of a primary mechanical injury followed by a prolonged secondary injury phase, which drives extensive cognitive, motor, and affective symptoms. Currently, no FDA-approved pharmacotherapeutics targeting TBI-induced secondary injury exist. A primary driver of secondary injury is dysfunctional neuroinflammation, which contributes to cellular disruption and cell death. The transcription factor NF-κB is a promising therapeutic target as it regulates the expression of multiple pro-inflammatory and cell-regulatory genes. We developed an elastin-like polypeptide (ELP)-delivered inhibitor of NF-κB (SynB1-ELP-p50i), which prevents NF-κB nuclear translocation. ELPs are non-immunogenic polypeptides that stabilize therapeutics in circulation and mediate their delivery to injury sites. This study assessed the pharmacokinetic profile (25-100 mg/kg) and biodistribution of SynB1-ELP-p50i, as well as its molecular and neurobehavioral efficacy, using the closed-head injury model of engineered rotational acceleration (CHIMERA) TBI system. Discovery-phase quantitative proteomics (LC/MS) was conducted to identify protein-level shifts following TBI and NF-κB inhibition. Analysis of SynB1-ELP-p50i revealed a terminal half-life of ~25 hours. Whole-organ *in vivo* imaging and fluorescent histology 12 hours post-treatment showed peak organ concentrations in subjects receiving the 100 mg/kg dose. Gene set enrichment analysis (GSEA) of the quantitative proteomics data revealed that TBI induced an acute inflammatory state accompanied by hyperactive mRNA processing and upregulated protein acylation networks (FDR < 0.05; |NES| > 2). NF-κB inhibition with SynB1-ELP-p50i eliminated the abrupt increase in mRNA processing and upregulated numerous processes relating to mitochondrial respiration and metabolic function, driven by electron transport chain and NADH dehydrogenase pathways (FDR < 0.05; |NES| > 2. Together, these data suggest that NF-κB inhibition following TBI is immune-modulatory and upregulates homeostatic metabolic processes. Ongoing neurobehavioral tests and immunohistochemical analyses are being conducted to further characterize NF-κB inhibition as a promising TBI therapeutic strategy.

Disclosures: J. Haskell: None.

Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.23/X31

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Funded by U.S. Department of Defense office of CDMRP. Grant award to K.R. Byrnes.

Title: Characterizing behavioral differences of chronic TBI mice using machine learning

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Abstract: Traumatic brain injury (TBI) is a debilitating condition that affects millions of people every year. Evidence of reduced brain glucose following TBI suggests that interventions that enhance brain glucose uptake may represent a therapeutic approach. Our lab and other labs have demonstrated the efficacy of intranasal insulin to reach the brain and to improve brain glucose uptake. In this study, female C57BL/6J mice underwent either controlled cortical impact injury or sham surgery, followed by a 1-week recovery period and 7 consecutive days of intranasal treatment with insulin (6IU) or saline (n = 11/group). We assessed several behavioral and biochemical outcomes, including locomotor activity and anxiety in the open field. 49 days post-injury (dpi), TBI mice exhibited significant hyperactivity in the open field compared with sham controls ($p < 0.05$), with no evidence of altered anxiety-like behavior. After identifying a significant increase in open-field activity in TBI mice, we conducted an exploratory follow-up analysis using newly available computational tools to further characterize this behavioral pattern. To achieve this, we used DeepLabCut, a pose estimation toolbox, to first track individual keypoints on mice for the duration of the five-minute open field assessment. This data was then analyzed using Keypoint MoSeq to learn and track stereotyped movement patterns, or syllables. Significant differences in the frequency of several syllables were evident in both the TBI-Sal and TBI-INS groups compared to Sham-Sal mice, while the insulin treatment had no effect. TBI mice turned right significantly more frequently than shams (all TBI mice were injured on the left cortex), and display significantly less freezing, looking left, and grooming ($p < 0.05$). Leveraging modern computational abilities we were able to break down motion in an open field into repeated syllables and detect significant differences between TBI and Sham mice providing novel depth to the understanding of hyperactivity in chronic TBI mice.

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Poster

PSTR053: Brain Injury: Animal Models: Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR053.24/X32

Topic: B.09. Glial Mechanisms

Support: JP25K10837

Title: The microglial changes of mitochondrial functions in the delayed carbon monoxide encephalopathy rat model

Authors: *S. OCHI[1], T. NISHIHARA[2], S. BOKU[3], J. IGA[4];
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Abstract: IntroductionDelayed carbon monoxide (CO) encephalopathy may occur following recovery after several weeks from acute CO poisoning. However, the mechanism of delayed neuronal injury remains unknown. We previously reported that the rat model of delayed CO encephalopathy showed cognitive impairment and hippocampal cell death, especially in the lesions of dentate gyrus. Furthermore, delayed CO encephalopathy caused the impairment of neural precursor cells and also the number of microglial cells and the mRNA expressions of several neurotrophic factors in the hippocampus were decreased. Microglia is known to play important roles in the adult neurogenesis and promoting neurotropic factors. Therefore, in the current study, we hypothesized that functional changes of microglia may be affected in delayed CO encephalopathy and investigated the mitochondrial respiration and glycolysis of microglia in delayed neuronal CO poisoning. Materials and Methods Wistar male rats (6 weeks old) were exposed to 1000 ppm CO for 40 min and then 3000 ppm for 20 min until they lost consciousness. If not, rats were exposed to 10000 ppm until they lost consciousness. Behavioral effects on learning and memory function were measured by the passive-avoidance test between control and CO treated rats until 3 weeks. After 3 weeks, rats were sacrificed, and we used magnetic cell sorting to obtain microglial cells from the hippocampus with the CD11b/c-microbeads antibody, and flow cytometry was performed to determine the purity of microglia. We investigated oxygen consumption rate and extracellular acidification rate to evaluate mitochondrial respiration and glycolysis, respectively, in rat primary microglial cells using XFp Extracellular Flux Analyzer between CO group (n = 6) and control group (n= 6). Student's T-test or Mann-Whitney U test were used for comparisons between control and CO groups. Significance was determined by P values <0.05. Results The latencies of passive avoidance test after 3 weeks were significantly shorter in the CO group than in the control group. Compared to control groups, basal respiration (24.4 pmol/min vs 16.8 pmol/min; p = 0.019), maximum

respiration (26.8 pmol/min vs 14.9 pmol/min; p = 0.001) and ATP production (18.5 pmol/min vs 12.5 pmol/min; p = 0.007) in CO group were significantly decreased after 3 weeks. Conclusions This study suggests delayed CO injury might damage microglia and it was affected at least 3 weeks. Thus, the impairment of functions of microglia may have important role in the pathogenesis of delayed CO encephalopathy.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.01/Y1

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Korea Drug Development Fund RS-2024-00335752
National Research Foundation of Korea (NRF) RS-2024-00408736

Title: Targeting Lipocalin-2 with a small-molecule inhibitor to suppress neuroinflammation

Authors: *J. KWON[1], J. LEE[2], J.-H. KIM[1], S. KWON[2], J.-E. PARK[2], J. HWANG[2], J. LEE[1], J. KIM[3], J. HWANG[4], H.-H. LIM[4], M. SONG[2], K. SUK[1];
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Abstract: Lipocalin-2 (LCN2) is a key pro-inflammatory mediator that is upregulated in various central nervous system (CNS) disorders, particularly in astrocytes. Despite its well-established role in neuroinflammation, LCN2-targeted therapeutic strategies for CNS diseases remain undeveloped. Therefore, this study aims to identify and characterize DN300653, a novel small-molecule LCN2 inhibitor, for its potential to treat neuroinflammation-induced CNS disorders. DN300653 effectively suppressed LCN2-induced proinflammatory chemokine and cytokine production by blocking LCN2-receptor interactions in cultured astrocytes. Additionally, DN300653 exhibited favorable blood-brain barrier permeability in a parallel artificial membrane permeability assay (PAMPA), suggesting its potential for CNS delivery, and its pharmacokinetic properties were analyzed prior to *in vivo* studies. *In vivo*, DN300653 significantly reduced clinical symptoms of experimental autoimmune encephalomyelitis (EAE) and lipopolysaccharide-induced acute neuroinflammation. This was accompanied by reduced inflammatory cytokine production, glial activation, and demyelination in the spinal cord and brain. DN300653 was effective under preventive conditions and therapeutic conditions, including when administered after EAE onset, indicating its potential to modulate established neuroinflammatory processes. Collectively, these findings suggest that DN300653 is a promising

therapeutic candidate and that pharmacological targeting of LCN2 may be a viable treatment strategy for CNS autoimmune and neuroinflammatory diseases.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.02/Y2

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Selective ROCK2 inhibitors ameliorate murine models of multiple sclerosis and demyelination by harnessing inflammation and restoring homeostasis

Authors: *J. MORETTI[1,2], W. CHEN[1,2], M. NYUYDZEFE[1,2], D. KEAHI[1,2], A. ALCANTARA[3], C. V. MELENDEZ-VASQUEZ[3], S. WAKSAL[1,2], A. ZANIN-ZHOROV[1,2]; [1]Translational Med., Graviton Biosci., New York, NY; [2]Graviton Biosci. BV, Amsterdam, Netherlands; [3]Hunter Col., New York, NY

Abstract: Multiple sclerosis (MS) is a chronic and progressive autoimmune disease affecting the central nervous system, characterized by demyelination of neurons in the brain, spinal cord and optic nerves. It results in an irreversible neurological decline, associated with physical disability and cognitive impairment. Rho-associated coiled-coil-containing protein kinases (ROCK) 1 and 2 are activated downstream of various receptors and stimuli and have common cellular outcomes, such as modulation of actin polymerization and pro-fibrotic effects. ROCK2 also specifically regulates key signaling pathways involved in proinflammatory immune responses. Selective ROCK2 inhibition has been shown to dampen inflammation in various tissues and pathologies, acting both in adaptive - autoimmune Th17, and innate immune cells - monocytes or Kupffer cells. However, whether selective ROCK2 inhibition has a therapeutic potential in MS has not been assessed. We therefore aimed to characterize the biological effects of ROCK2 selective inhibitors in MS and demyelination in preclinical animal models. We generated ROCK2 selective small molecule inhibitors, tested them in Experimental Autoimmune Encephalomyelitis (EAE) murine model of MS and analyzed the clinical outcomes and biomarkers of the disease. We also used non-autoimmune Cuprizone-induced demyelination murine models to study demyelination and remyelination in vivo. We further assessed the mechanisms of action of the inhibitors in various ex-vivo experiments, testing the role of ROCK2 inhibition in oligodendrocytes, neurons and microglia biology. Our study shows that therapeutic oral administration of novel BBB-penetrant selective ROCK2 inhibitors ameliorates limb paralysis and reduces the clinical scores in EAE model. ROCK2 inhibition improves the demyelination score, decreases inflammation in the spinal cord and improves biomarkers of neurodegeneration. Selective ROCK2 inhibitors also prevent Cuprizone-induced demyelination

in mice. Ex vivo, ROCK2 targeting directly promotes myelinating capacity in oligodendrocytes, upregulates phagocytosis of myelin residues by microglia, and promotes neurite growth. Altogether, our results highlight the therapeutic potential of selective ROCK2 inhibitors in MS, which concurrently rebalance disease-associated inflammation and prevent demyelination in vivo, promotes remyelination by oligodendrocytes and restore cell and tissue homeostasis.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.03/Y3

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Texas Woman's University Woodcock Institute Research Grant

Title: The striatum and ventromedial prefrontal cortex modulate the subjective value of cognitive performance feedback in individuals with multiple sclerosis

Authors: *C. J. CAGNA[1,3], K. SUCICH[2], E. DOBRYAKOVA[2,3];
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Abstract: Cognitive impairment impacts up to 90% of people with multiple sclerosis (MS). As a result, people with MS often undergo cognitive rehabilitation. To maximize rehabilitation outcomes, participants must effectively learn from feedback about their performance throughout treatment and regulate their performance accordingly. The utility of this feedback, however, will be limited if the learner does not value the information it provides. The ventral striatum (VS), caudate nucleus (CN), and ventromedial prefrontal cortex (vmPFC) process performance feedback information to promote learning. They also represent the subjective value of a stimulus and guide motivated behavior towards it. Willingness-to-pay (WTP) paradigms empirically assess subjective value by presenting participants with decisions to obtain a prospective reward in exchange for a cost (e.g., money). Given the overlapping roles of the VS, CN, and vmPFC in feedback processing and subjective valuation, the current study examined their roles in modulating feedback value in people with MS. Fifteen individuals with relapsing-remitting MS [9 females, 6 males; M_{age} = 52.00 (11.01)] completed a WTP verbal associative memory task, which measured feedback valuation by assigning monetary costs to feedback. During functional magnetic resonance imaging, participants made decisions about whether to purchase accuracy feedback while learning word pairs, with the knowledge that they would earn a monetary bonus contingent on their performance during a future test phase. Any feedback purchases made during learning were deducted from test performance winnings. *A priori* region-of-interest and whole-

brain analyses revealed reduced right CN activity during decisions to decline feedback. Generalized psychophysiological interaction analysis revealed stronger functional connectivity between the vmPFC and reward-related regions (VS), verbal-learning-related regions (left medial temporal gyrus), thalamus, and left insula during decisions to purchase feedback, compared to decisions to decline it. Furthermore, a generalized logistic mixed model indicated that this stronger vmPFC connectivity predicted a higher likelihood of purchasing feedback, independent of the influences of age, education, sex, task fatigue, feedback cost, and confidence [$X^2(1) = 5.23$, $p = .02$, $b = 9.02$, $b_{SE} = 3.58$]. Our findings provide neural evidence of corticostriatal value regions encoding feedback value and facilitating motivated learning from it. They also identify potential neural targets for modulating feedback valuation, enhancing feedback learning, and improving rehabilitation outcomes for people with MS.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.04/Y4

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Catalyst funded by Shirley Ryan AbilityLab

Title: Effect of Acute Intermittent Hypoxia Combined with Neuromuscular Electrical Stimulation on Corticospinal Excitability in Individuals with Multiple Sclerosis

Authors: *S. YAN[1], H. HASSANLOUEI[2], K. MANNELLA[2], L. OSHEA[3], A. NEHRUJEE[5], H. LIM[6], M. S. SANDHU[4];
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Abstract: Background: Multiple sclerosis (MS) commonly causes persistent motor impairments, including lower-extremity weakness and foot drop. Although disease-modifying therapies can reduce relapse activity, existing motor deficits often require rehabilitation, and current interventions have limited effectiveness. Neuromuscular electrical stimulation (NMES) may improve motor function by increasing corticospinal excitability, while acute intermittent hypoxia (AIH) may promote neuroplasticity through serotonergic and brain-derived neurotrophic factor dependent pathways. Combining AIH with NMES may therefore enhance rehabilitation-induced motor recovery in individuals with MS. This study examined whether AIH combined with repetitive common peroneal nerve stimulation improves maximum ankle torque and corticospinal excitability of the ankle dorsiflexors in individuals with relapsing-remitting MS. **Methods:** Ten able-bodied adults and ten adults with relapsing-remitting MS completed three

randomized intervention conditions in a single blinded, cross-over design: AIH+NMES, NMES alone, and AIH alone, separated by a one-week washout. AIH consisted of 15 brief hypoxic episodes, each lasting up to one minute, followed by periods of normoxia. NMES was delivered to the tibialis anterior for 30 minutes at 40 Hz and an intensity of 2-3 times the sensory threshold. Outcomes were assessed pre- and post-intervention and included ankle dorsiflexion and plantarflexion torque and motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). **Results**: In the MS group, plantarflexion torque increased by 19% after AIH alone, 5% after AIH+NMES, and 9% after NMES alone, while dorsiflexion changed by -6%, -13%, and -4%, respectively. Torque changes in control participants were minimal. MEP amplitude increased in the MS group following all interventions, with the greatest increases observed after AIH+NMES and AIH alone, 14.9% and 13.1%, respectively, compared with a 2.4% increase after NMES alone. In the control group, MEP amplitude showed smaller changes, increasing by 5.8% after AIH+NMES and 1.6% after AIH alone, while decreasing by 5.8% after NMES alone. **Conclusion:** Our preliminary findings suggest that AIH-based interventions are associated with increased corticospinal excitability in MS group, but not in controls, while ankle torque responses are variable. The results identify AIH as the likely driver and support a larger powered trial pairing AIH with task-specific training.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.05/Y5

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant F30EY036256

Title: Targeting neuronal protease-activated receptor 1 confers neuroprotection in models of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by immune cell infiltration, demyelination, and neuronal damage. Disease modifying therapies targeting the immune system reduce relapses that slows but does not prevent progression. Thus, understanding mechanisms of neuronal damage in MS may provide novel therapeutic targets. To that end, human induced pluripotent stem cell-derived motor neurons (iPSC motor neurons) were treated for two hours with lysates from lymphokine activated killer (LAK) cells which resulted in microtubule destabilization visualized as a “beads-on-a-string” pattern after staining with β_3-tubulin. The rapid kinetics of the response are consistent with activation of a G-protein coupled receptor (GPCR), leading to the hypothesis that GPCR

signaling leads to neuronal microtubule damage. Given the abundance of proteases in LAK cell lysates, protease-activated receptors (PAR), a family of four GPCRs activated by proteolytic cleavage, were considered strong candidate receptors. PAR1 emerged as the leading candidate due to high expression in iPSC motor neurons. Both thrombin, a potent PAR1 agonist, and the PAR1-selective peptide agonist TFLLRN induced microtubule destabilization in iPSC motor neurons. In addition to neurons, PAR1 is expressed on endothelial cells, immune cells, and in humans, platelets. To better understand the contribution of neuronal PAR1 signaling, bone marrow chimeras were generated using wild-type (WT) and *F2r* (PAR1) global knock-out (KO) mice to create mice with PAR1 deficiency specific to non-immune cells (WT->*F2r*) with WT->WT as controls. When experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, was induced in the chimeras, disease onset was comparable to WT->WT, indicating that CNS infiltration of pathogenic T cells was intact across the PAR1-deficient endothelium. However, EAE disease severity was significantly attenuated in the WT->*F2r* chimeras, implicating PAR1 in driving neuronal damage. To test whether PAR1 antagonism could protect in EAE, the FDA-approved PAR1 antagonist vorapaxar was administered after EAE onset for five consecutive days. EAE disease severity was attenuated in WT, but not, *F2r* KO mice. This dosing regimen provided a neuroprotective benefit without off-target effects using a limited time course, which is critical for clinical translation since long-term use of vorapaxar in humans is associated with bleeding risks. Collectively, these findings identify neuronal PAR1 as a key mediator of neuronal damage and support PAR1 antagonism as a potential neuroprotective strategy in MS.

Disclosures: K.C. Sommers: None. **B.N. Dittel:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.06/Y6

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH R01 NS120877
NIH R21 NS107946
NMSS RG1901-33209
the MN State SCI and TBI Program
the Mayo Clinic Center for Regenerative Biotherapeutics

Title: PAR1 Restrains Neural Stem Cell Engraftment and Oligodendrocyte Differentiation During Myelin Repair

Authors: *C. CHOI[1], W. SIMON[2], H. YOON[1,3], J. CAREY[2], K. KAWATANI[4], T. KANEKIYO[4,5], I. A. SCARISBRICK[1,5,3,2];
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[4]Neurosci., Mayo Clin., Jacksonville, FL; [5]Ctr. for Regenerative Biotherapeutics, Mayo Clin., Rochester, MN

Abstract: Protease-activated receptor 1 (PAR1) is a thrombin receptor implicated in central nervous system injury responses, but its role in neural stem cell (NSC) fate and remyelination is not fully defined. We tested whether PAR1 limits the regenerative capacity of adult subventricular zone (SVZ)-derived NSCs using *in vivo* transplantation, transcriptomics, proteomics, human induced pluripotent stem cell (iPSC)-derived cerebral organoids, and pathway-directed pharmacology. GFP+ PAR1+/+ or PAR1-/- murine SVZ NSCs were bilaterally microinjected into intact or cuprizone-demyelinated corpus callosum of 12 wk female C57BL6J mice and analyzed 4 weeks later. PAR1-/- NSCs showed increased engraftment and dispersion, with 1.5-fold higher GFP+ cell counts in intact corpus callosum and 1.7-fold higher counts in demyelinated corpus callosum. PAR1 loss also increased migration distance in both environments. Immunophenotyping showed enhanced oligodendrocyte lineage progression, most prominently after demyelination: PAR1-/- grafts had increased Ki67+ cells that were largely SOX2-negative, increased PDGFRα+ oligodendrocyte progenitors, and increased ASPA+ mature oligodendrocyte-lineage cells. PAR1-/- NSCs in demyelinated corpus callosum also showed increased OLIG2 and HMGCS1 co-expression, linking PAR1 loss to cholesterol biosynthesis in the oligodendrocyte lineage. Bulk RNA sequencing and tandem mass tag proteomics of proliferating NSCs and 3-day differentiated NSCs identified genotype-dependent regulation of genes and proteins involved in myelination, extracellular matrix organization, integrin signaling, Rho GTPase signaling, PI3K/AKT, WNT/β-catenin, growth factor signaling, and lipid metabolism. Key oligodendrocyte and myelin-associated transcripts, including *Sox10*, *Myrf*, *Mbp*, *Plp1*, *Mog*, *Mag*, *Cnp*, *Ugt8a*, and *Bcas1*, were increased by PAR1 knockout. Pharmacological PAR1 inhibition with vorapaxar in human iPSC-derived cerebral organoids recapitulated activation of myelination signaling and overlapping cytoskeletal, extracellular matrix, and growth factor pathways, supporting translational conservation. Mechanistically, PAR1-/- NSCs showed increased *Ntrk2* expression and CREB activation; inhibition of TrkB or CREB attenuated PAR1-dependent increases in *Mbp* and *Plp1*, with combined blockade reducing induction of *Pdgfrα*, *Mbp*, *Plp1*, *Myrf*, and *Ugt8a*. Together, these findings identify PAR1 as a molecular brake on NSC engraftment, migration, and oligodendrocyte differentiation. Targeting PAR1 may improve NSC-based strategies for myelin repair.

Disclosures: C. Choi: None. **W. Simon:** None. **H. Yoon:** None. **J. Carey:** None. **K. Kawatani:** None. **T. Kanekiyo:** None. **I.A. Scarisbrick:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.07/Y7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: R01NS124123-05

Title: Contribution of IRE1α to disease phenotypes during EAE, a rodent model of Multiple Sclerosis

Authors: *E. JONES[1], A. MCDERMOTT[3], K. NGUYEN[2], J. R. BETHEA[4];
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Abstract: Multiple Sclerosis (MS) is the most common cause of neurological disability in people aged 20-40 that does not stem from trauma or injury. Patients experience a heterogeneous symptom burden, with motor disability (~90%) and cognitive dysfunction (40-70%) being among the most prominent experienced. Notably, inositol-requiring enzyme 1α (IRE1α) serves as a novel biological pathway that may work to alleviate both of these symptoms concomitantly. IRE1α is a transmembrane protein located on the ER lumen that senses ER stress from perturbed proteostasis and initiates cellular programs to restore homeostasis. Published work demonstrates that CRISPR generated C148S mice, which have global, augmented IRE1α signaling, have reduced inflammatory burden during an experimental model of MS compared to WT animals. When coupled with literature demonstrating that IRE1α signaling positively regulates cognitive performance, learning, and memory, these findings position IRE1α as a compelling candidate for investigation in the context of MS-induced motor disability and cognitive dysfunction. In these studies, we induced experimental autoimmune encephalomyelitis (EAE), a rodent model MS, combined with CRISPR generated and cell-specific transgenic mice to elucidate the role of ER stress sensor IRE1α in EAE-induced motor and cognitive phenotypes in both sexes. Daily motor scoring and open field testing were used to assess motor disability. Novel object recognition (NOR) and fear conditioning (FC) were utilized to evaluate cognitive performance. CRISPR-generated C148S mice demonstrate remarkable amelioration of motor disease during EAE across sexes compared to WT EAE animals. With improvement of the motor phenotype, there was also a reduction in protein expression of neuroinflammatory markers, Iba1, and Gfap in the lumbar spinal cord of C148S EAE animals. In addition, male C148S EAE mice trended towards improved cognitive performance compared to WT EAE animals on NOR. Given the role of microglia in orchestrating inflammatory responses in the central nervous system (CNS), we wanted to further explore these findings by inducing EAE and a conditional genetic knockout of microglial IRE1α hypothesizing that abrogating IRE1α signaling in microglial cells will worsen EAE motor and cognitive phenotypes. Together, these results reveal the role of global, as well as microglial IRE1α signaling in EAE-induced motor and cognitive dysfunction, which may translate and inform the development of new disease-modifying treatments (DMT) for MS patients.

Disclosures: E. Jones: None. **A. McDermott:** None. **K. Nguyen:** None. **J.R. Bethea:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.08/Y8

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R01NS124123

Title: Pharmacological inhibition of ERO1α attenuates motor disease in the experimental autoimmune encephalomyelitis mouse model of multiple sclerosis.

Authors: *A. MCDERMOTT[1], E. JONES[3], B. J. KERR[5], J. R. BETHEA[2], K. NGUYEN[4]; [2]Anat. and Cell Biol., [1]The George Washington Univ., Washington, DC; [3]Anat. and Cell Biol., George Washington Univ., Washington DC, DC; [4]Anat. and Cell Biol., George Washington Univ., Washington, DC; [5]Anesthesiol., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Endoplasmic reticulum oxidoreductase 1 alpha (ERO1α) is a critical regulator of oxidative protein folding in the endoplasmic reticulum by working with protein disulfide isomerase to form disulfide bonds in nascent proteins, a process that generates reactive oxygen species (ROS). When dysregulated, ERO1α activity can lead to excessive ROS production, hyperoxidation, and protein misfolding, all of which have been shown to act as pathological drivers of illness and/or disease. Pathogenic activity of ERO1α has been linked to cancer growth and progression; however, its role in multiple sclerosis (MS) remains understudied. To study the role of ERO1α in MS, we used an experimental autoimmune encephalomyelitis (EAE) rodent model of MS. We performed open-field motor scoring to assess locomotor impairment and von Frey testing to measure mechanical hypersensitivity as an indicator of pain. Since the lumbar spinal cord is critically targeted during disease initiation due to breakdown of the blood-spinal cord barrier and infiltration of activated immune cells, we wanted to determine if there was a change in ERO1α protein expression in this region. We found that there was a significant increase in ERO1α activity in the lumbar spinal cord of EAE mice compared to controls, which was attenuated with EN460 treatment. Although preclinical disease modifying therapies evaluated in EAE have successfully attenuated motor disease severity, complete and sustained prevention of motor pathology has rarely been achieved. When we treated EAE mice with an ERO1α inhibitor (EN460) at the onset of chronic pain (9-10 days post EAE onset), motor dysfunction was completely prevented in females and was reduced by 67% in males. Interestingly, ERO1α inhibition also elicited sexually dimorphic protection against chronic neuropathic pain, where female EAE mice showed an acute rescue and males exhibited sustained protection. These results suggest that pharmacological inhibition of Ero1α modulates specific pathways involved in EAE pathology. Further studies will focus on generating a whole-body murine knockout of ERO1α in which we will induce EAE to see if pharmacological data can be recapitulated using a genetic approach paired with biochemical tools to further investigate cell-specific mechanisms of protection governed by ERO1α inhibition.

Disclosures: A. McDermott: None. **E. Jones:** None. **B.J. Kerr:** None. **J.R. Bethea:** None. **K. Nguyen:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.09/Y9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Department of Biology, start-up grant
Department of BMCE, start-up grant

Title: Dissecting Inflammatory and Metabolic Drivers of Neurodegeneration in Secondary Progressive Multiple Sclerosis

Authors: *T. H. RIYED[1], J. ZENG[2], C. LO[3];
[1]Biomed. and Chem. Engin., syracuse university, Syracuse, NY; [2]Biomed. and Chem. Engin., [3]Biol., Syracuse Univ., Syracuse, NY

Abstract: Secondary progressive multiple sclerosis (SPMS) is a clinically intractable stage of MS marked by progressive disability despite reduced relapse activity. Although inflammatory and metabolic dysfunction are recognized, how these processes converge to sustain disease progression remains unclear. Here, we performed integrated transcriptomic and mechanistic analyses to define convergent molecular networks in SPMS and identify targetable nodes. Analysis of bulk transcriptomic data from post-mortem SPMS cortical grey matter (GSE131282) revealed coordinated dysregulation of mitochondrial, lysosomal-autophagy, inflammatory, and ferroptosis-related pathways. This included downregulation of oxidative phosphorylation and mitochondrial dynamics genes, reduced expression of lysosomal and autophagy regulators, and altered ferroptosis-associated mediators (ACSL4, GPX4, LGALS3, RAP1B, TMEM106B, OPA1). Concurrently, we observed increased p62 accumulation and enrichment of chronic NF-κB and interferon-response programs. Together, these findings define a convergent state in which lysosomal-autophagy failure links mitochondrial dysfunction with sustained inflammatory signaling. We validated this integrated signature in a myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE) mouse model. Molecular and histological analyses confirmed reduced metabolic and structural markers, along with persistent elevation of p62 and phosphorylated NF-κB signaling, consistent with a chronic progressive-like disease state. To functionally test therapeutic entry points within this network, we evaluated two brain-targeted strategies: a BBB-penetrating anti-inflammatory peptide and a BBB-penetrating lysosomal-restoring nanoparticle. While the peptide effectively reduced NF-κB activation (p-p65), lysosomal restoration produced broader network rescue, including clearance of p62 accumulation, recovery of mitochondrial structural integrity (OPA1), and improved cellular homeostasis. These findings demonstrate that targeting either chronic inflammation or lysosomal-autophagy failure can disrupt progressive neuroinflammation, establishing both BBB-penetrating peptides and functional nanoparticles as distinct, highly viable therapeutic strategies for progressive MS.

Disclosures: T.H. Riyed: None. **J. Zeng:** None. **C. Lo:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.10/Y10

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Epstein-Barr Virus-Associated Immune and Virological Profiles in Multiple Sclerosis Patients Receiving High Efficacy Therapies

Authors: *R. PILLAI, J. LIN, E. JOHNSTON, S. BREWI, R. ALFONSO, S. A. SADIQ; Tisch MS Res. Ctr. of NY, New York, NY

Abstract: Epstein-Barr virus (EBV) is considered one of the strongest environmental factors associated with multiple sclerosis (MS), yet the mechanisms linking viral infection to disease activity remain incompletely understood. Because highly effective disease-modifying therapies (DMTs) profoundly alter immune function and leukocyte trafficking, they may also influence host control of latent EBV infection. To investigate this possibility, we characterized EBV-associated immune and virological profiles in healthy controls (HC, n=25), untreated MS patients (n=19), anti-CD20-treated MS patients (n=32), and natalizumab-treated MS patients (n=21). Serological responses against EBV viral capsid antigen (VCA) and EBV nuclear antigen 1 (EBNA1) were measured by ELISA, while peripheral blood mononuclear cells were stimulated ex vivo with EBV- and cytomegalovirus-derived overlapping peptide pools and antigen-specific T-cell responses were quantified by IFNγ and IL-2 FluoroSpot assays. In parallel, EBV DNA was assessed in peripheral blood using quantitative PCR-based approaches. Anti-EBV antibody titers were broadly comparable among groups. Likewise, untreated MS patients exhibited EBV-specific T-cell responses comparable to those observed in healthy controls. In contrast, marked therapy-associated differences emerged among patients receiving high-efficacy DMTs. Anti-CD20-treated patients exhibited reduced frequencies of EBV-reactive cytokine-producing T cells together with lower EBV DNA detection, consistent with diminished peripheral antiviral immune activity. Conversely, natalizumab-treated patients demonstrated enhanced EBV-specific T-cell responses and increased EBV DNA positivity. Notably, cytomegalovirus-specific responses did not exhibit the same treatment-associated pattern, suggesting a relative enrichment of EBV-related immune alterations. These findings indicate that highly effective MS therapies are associated with distinct EBV-specific immune and virological signatures and support the concept that DMT-dependent immune modulation may differentially influence peripheral control of latent EBV infection. Further investigation of EBV-host interactions in treated and untreated MS may provide insight into mechanisms linking viral persistence, immune regulation, and disease pathogenesis.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.11/Y11

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: National Multiple Sclerosis Society

Title: Neural Indices of Cognitive Fatigability During Ongoing Processing Speed Task Performance in People with Multiple Sclerosis

Authors: *M. TRIPOLI BALKO[1], H. NYARADY[1], T. J. COVEY[2];
[2]Pharmacol. and Toxicology, [1]Jacobs Sch. of Med. and Biomed. Sciences, State Univ. of New York at Buffalo, Buffalo, NY

Abstract: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. The symptoms resulting from MS can vary widely, and commonly include cognitive impairment, fatigue, motor deficits, pain in extremities, and tingling or numbness. Among these symptoms, fatigue is reported to affect around 90% of people with MS and is described as the most debilitating symptom for the majority of people. Fatigue in MS often manifests as cognitive fatigue, or the experience of complete mental exhaustion, and is distinct from the fatigue felt by the average person or a lack of quality sleep. Cognitive fatigue can be characterized by the perception of fatigue during cognition, or as "fatigability" which is the exacerbation of fatigue during cognitive task performance. In the present study, we identified novel indices of cognitive fatigability during ongoing performance of a processing speed task in people with MS. We hypothesized that people with MS would demonstrate a steeper decline in cognitive performance as a function of time-on-task in comparison to healthy control participants. Study participants completed a computerized Symbol Digit Modalities Test (cSDMT), which was adapted from a neuropsychological test that is well validated for MS. Response speed was recorded for each trial, and event-related potentials (ERPs) were derived from ongoing electroencephalographic (EEG) data recorded during task performance. The behavioral findings of the present study provide preliminary evidence that cognitive fatigue diminishes the benefits of increasing task efficiency with increased time-on-task in people with MS. ERP component amplitude was relatively stable in the control group for the duration of task performance, whereas amplitudes for the MS group fluctuated throughout the task. For earlier, exogenously driven ERP components, P1 and N1, there was a change in component amplitude in MS compared to controls that was most pronounced midway through the task, and a return to baseline with increased time-on-task. For later, endogenously driven ERP components, N2 and P3, there was a change in component amplitude that exhibited a plateau with increased time on task. ERPs may therefore serve as sensitive indices of the induction of cognitive fatigue with increased time-on-task in PwMS, with distinct ERP components providing insight into fluctuations in brain mechanisms that seek to compensate for increasing fatigue during sustained cognitive performance. The present findings identify novel biomarkers that can enable more precise management of fatigue symptoms in PwMS.

Disclosures: M. Tripoli Balko: None. **H. Nyarady:** None. **T.J. Covey:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

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Program #/Poster #: PSTR054.12/Y12

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R16NS129748

Title: Neural stem cells attenuate neuroinflammation in an EAE mouse model of multiple sclerosis

Authors: *G. CHAUDHRY[1], **F. SYED**[2], Y. JIMOH[1], S. KOJAN[3];
[1]Oakland Univ., Rochester, MI; [2]Oakland Univ., Rochester Hills, MI; [3]Corewell Hlth., Rochester, MI

Abstract: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that damages the myelin sheath, leading to neurological dysfunction. There is a significant need for therapies that combine immunomodulation and neuroprotection. Mesenchymal stem cells (MSCs) and neural stem cells (NSCs) have been shown to regulate inflammation and support tissue repair. Our previous studies indicated that NSCs are more effective than MSCs at reducing disease severity and promoting recovery in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. In this study, we explored the mechanisms by which NSCs modulate neuroinflammation in mice with EAE. Mice with EAE received intravenous treatments with either MSCs or NSCs. The animals underwent daily neurobehavioral assessments until sacrifice, after which brain, spinal cord, blood, and eye samples were collected for biochemical, cellular, and molecular analyses. The results demonstrated significant improvements across multiple measures following treatment with both MSCs and NSCs in an EAE model. Notably, NSCs were more effective, as they not only reduced disease severity but also enhanced recovery compared with diseased animals. Structural improvements were highlighted by H&E staining, which revealed improved tissue architecture in the central nervous system and reduced inflammatory pathology, including reduced perivascular cuffing. This improvement was particularly notable in the NSC-treated group, where hippocampal pyramidal cell organization was more orderly than in animals treated with MSCs. Immunofluorescence analysis indicated that untreated EAE mice exhibited activated astrocytes and microglia, as evidenced by GFAP and IBA1/CD68 staining. However, these activation markers were significantly reduced after cell treatment, with the most pronounced effect in NSC-treated mice, indicating reduced astrogliosis and microglial activation. This suggests that NSC therapy effectively attenuated the neuroinflammatory response. Additionally, NSC-treated mice exhibited enhanced remyelination, as evidenced by stronger myelin basic protein staining than in MSC-treated animals, underscoring the superior therapeutic potential of NSCs in this context. These results lay the groundwork for developing strategies to translate NSC-based MS treatments from preclinical to clinical applications.

Disclosures: G. Chaudhry: None. **F. Syed:** None. **Y. Jimoh:** None. **S. Kojan:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.13/Y13

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Coping, personality, and perceived cognition in multiple sclerosis: Acceptance as a protective factor for fatigue and cognition burden

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Abstract: Cognitive dysfunction and fatigue are among the most disabling manifestations of multiple sclerosis (MS), yet individuals vary substantially in how they adapt to these challenges. We examined relationships among coping strategies, personality traits, fatigue severity, and perceived cognitive functioning in adults living with MS. A sample of 50 Canadian adults with a self-reported diagnosis of MS, the majority of whom were women, completed an online survey using validated psychometric measures: an MS-adapted Brief-COPE (Coping Orientation to Problems Experienced), the Ten-Item Personality Inventory, the Fatigue Severity Scale, and a measure of everyday cognitive failures. Participants also provided narrative accounts of adapting to MS. Quantitative data were analyzed using multiple regression models, while qualitative responses were examined using reflexive thematic analysis. Regression models accounted for significant variance in fatigue severity ($p < .01$) and perceived cognitive failures ($p < .01$). Acceptance was associated with lower fatigue and fewer cognitive failures ($p < .05$). Behavioural disengagement and self-blame were associated with greater fatigue and cognitive failures ($p < .05$), and lower emotional stability was associated with greater fatigue ($p < .05$). Qualitative analyses identified several themes, including biographical disruption, chronic vigilance, effortful self-management, and acceptance as a gradual and relational process. Participants described adaptation as an ongoing negotiation of uncertainty, identity, and symptom management. These findings support a process-oriented model of neurocognitive adaptation in MS in which acceptance may mitigate fatigue and cognitive burden, whereas self-blame and behavioural disengagement may amplify symptom-related challenges. Acceptance may represent an important target for clinical and rehabilitation-focused interventions.

Disclosures: S. Eskandari: None. **L. Schimanski:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.14/Y14

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: FAPESP 2023/02615-4
FAPESP 2023/15760-2

Title: Therapeutic potential of FGF-2 delivery strategies in experimental autoimmune encephalomyelitis: immunomodulatory and neuroprotective effects

Authors: *S. J. ORTIZ PEÑUELA[1], S. PINTO SANTOS[2], A. MIDORI ROSSI TOMIYAMA[2], S. KYRYLENKO[3], L. P. CARTAROZZI[2], A. L. OLIVEIRA[2];
[2]Structural and Functional Biol., [1]Univ. of Campinas - Lab. of Nerve Regeneration, Campinas, Brazil; [3]Biomed. Res. Ctr., Sumy, Ukraine

Abstract: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by progressive neurodegeneration. Given the limitations of current therapies, it is essential to explore new approaches with neuroprotective and immunomodulatory potential. Experimental autoimmune encephalomyelitis (EAE) in C57BL/6J mice represents a well-established model for investigating innovative therapeutic strategies. Fibroblast Growth Factor 2 (FGF-2) is a pleiotropic molecule with recognized neurotrophic and immunomodulatory activity. In this study, we evaluated two distinct FGF-2 delivery strategies: (1) a commercial variant (FGF2-STAB®) with enhanced thermal stability; and (2) a genetically engineered hESC line overexpressing the 31 kDa FGF-2 isoform upon doxycycline stimulation (hESCs-On FGF2). To distinguish the effects of cell transplantation from FGF-2-specific ones, a transgenic counterpart without FGF-2 overexpression (hESCs-Off FGF2) was included. Mice were immunized with $MOG_{35–55}$, and all treatments were initiated via intraperitoneal (FGF2-STAB®) or intravenous (hESCs) infusion on the day of immunization (CEUA/IB/UNICAMP, No. 6631-1/2025). Animals were monitored for body weight loss, clinical score, and gait parameters (CatWalk system) until 30 days post-induction (dpi). To evaluate the impact of treatments on the early inflammatory response, RT-qPCR was performed at 7 dpi to detect pro- and anti-inflammatory cytokines. No significant differences were observed among groups at this time point. At 14 dpi, flow cytometry was performed to evaluate the inflammatory profile, including astrocyte and microglial activation as well as lymphocyte populations. After 30 dpi, the lumbar spinal cord was collected for immunohistochemical analysis. The results demonstrated significant attenuation of clinical symptoms in all treated groups (Vehicle: 1.57, FGF2-STAB®: 0.87, hESCs-On FGF2: 0.89, and hESCs-Off FGF2: 1.01; $p<0.0001$). There was also improvement in gait performance (Regularity Index, $p<0.0001$), reduced glial reactivity, and synaptic preservation in Rexed lamina IX. In parallel, extracellular vesicles (EVs) derived from hESCs-On FGF2 cells have been isolated and characterized. Experiments are currently underway to evaluate EVs' independent therapeutic potential as a cell-free strategy. Taken together, these findings reveal the therapeutic potential of FGF-2, both in its thermostable form and as a product of transgenic human stem cells. The findings also underscore the intrinsic value of cell therapy and pave the way for EV-based neuroprotective therapies in multiple sclerosis.

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Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

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Program #/Poster #: PSTR054.15/Y15

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R01 NS120877
NIH Grant R21NS107946
National MS Society Grant RG1802-30121

Title: PAR1 Inhibition Reshapes Inflammatory and Lipid Signaling Networks to Support Myelin Preservation and Oligodendrocyte Maturation in EAE

Authors: *W. L. SIMON[1], H. YOON[2], M. NAIR[3], M. R. LANGLEY[4], I. SCARISBRICK[4]; [1]Mayo Clin. Grad. Sch. of Biomed. Sci., Rochester, MN; [2]Physical Med. & Rehabilitation, Rehabil. Med. Res. Ctr., [4]Physical Med. and Rehabil., [3]Mayo Clin., Rochester, MN

Abstract: Demyelinating diseases such as multiple sclerosis involve chronic neuroinflammation, disrupted lipid metabolism, and impaired myelin repair. Protease Activated Receptor 1 (PAR1), the thrombin receptor, regulates neuroinflammation, myelin dynamics, and CNS lipid homeostasis. Our prior studies show PAR1 genetic deletion accelerates developmental myelination and promotes myelin regeneration in lysolecithin and cuprizone demyelination models. Therefore, we hypothesized that pharmacologic PAR1 inhibition would reduce disease severity and enhance repair in the highly inflammatory MOG35-55 experimental autoimmune encephalomyelitis (EAE) demyelination model. Adult (12 wk) male and female C57BL6/J mice received daily intraperitoneal injections of vehicle or one of two PAR1 small-molecule antagonists (FDA-approved PAR1 inhibitor: vorapaxar; or SCH79797), from the onset of EAE clinical scores (Day 10 post-immunization) until the experimental endpoint (Day 30). EAE clinical scores showed significantly attenuated disease severity in male vorapaxar or SCH79797 versus vehicle recipients. Inclined plane testing showed significant improvements in motor function in male vorapaxar over vehicle recipients. In male spinal cords, vorapaxar treatment significantly reduced the number of demyelinated lesions, IBA1+ microglia/macrophages, and CD3+ T cells, while increasing myelin basic protein expression and preserving axons. Vorapaxar or SCH79797 treatment resulted in elevated numbers of mature GST3+ oligodendrocytes in both sexes. Of interest given PAR1's role in CNS lipid homeostasis and inflammation, vorapaxar significantly reduced microglial PLIN2—a marker of lipid droplet accumulation associated with neurodegeneration—in male spinal cords. MOG35-55 recall responses in splenocyte/lymph node preparations further support PAR1's immunomodulatory role. In a complementary experiment, Ribotag::PDGFRα-Cre female mice were treated with vorapaxar or vehicle and RNA sequencing performed on bulk and PDGFRα+ (oligodendrocyte-enriched) mRNA. Transcriptomic analysis showed altered expression of genes regulating inflammation, lipid metabolism, extracellular matrix remodeling, and cellular signaling toward a pro-repair landscape. Notably, vorapaxar treatment significantly downregulated Plin2 gene expression. These data demonstrate pharmacological PAR1 inhibition alters the inflammatory and lipid environment to foster an

environment conducive to myelin preservation and repair, underscoring PAR1 as a promising therapeutic target for demyelinating and potentially broader neurodegenerative conditions.

Disclosures: W.L. Simon: None. **H. Yoon:** None. **M. Nair:** None. **M.R. Langley:** None. **I. Scarisbrick:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.16/Y16

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch Multiple Sclerosis Research Center of New York (private funds)

Title: Primary progressive multiple sclerosis antibodies drive divergent neuronal and myelin pathology in human cerebral and spinal cord organoids

Authors: *D. KANGRIWALA, A. GRINBERG MITIDIERI, E. T. L. LYNCH, K. KALPANA, J. LIN, J. K. WONG, S. A. SADIQ;
Tisch MS Res. Ctr. of NY, New York, NY

Abstract: Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the CNS, presenting clinically distinct subtypes including relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive MS (SPMS). Progressive forms are characterized by sustained neurological decline, but whether the same underlying neurodegenerative mechanisms occur in the brain vs. the spinal cord, and in PPMS vs. SPMS remain unknown. We previously showed that antibodies in PPMS cerebrospinal fluid (CSF) possess unique pathogenic properties which distinguish them from RRMS and SPMS antibodies, with only PPMS antibodies inducing motor deficits and MS-related pathology in a mouse model (Wong et al., 2023). Our recent in vitro studies also show that antibodies in PPMS CSF induce degeneration of primary spinal cord neurons but not cortical neurons. To investigate whether PPMS antibodies exert distinct, region-specific effects on human neural tissue, we generated cerebral and spinal cord organoids from induced pluripotent stem cells (iPSCs) obtained from healthy individuals. Human iPSCs were guided through neural induction, matrix embedding, and extended maturation. Recombinant antibodies (rAbs) were derived from PPMS and SPMS patient CSF following B-cell isolation via FACS, PCR sequencing, plasmid expression, and purification. Cerebral organoids were treated with 10μg/mL rAbs at day 43; spinal cord organoids were treated at day 64. Organoids were fixed at 4 days post-treatment, then stained for MAP2, MBP, Olig2, and Luxol Fast Blue (LFB). All imaging and quantification were performed blinded. PPMS rAbs induced a significant reduction in MAP2 intensity in spinal cord organoids but not cerebral organoids, while SPMS rAbs had no effect on MAP2 in either organoid type. Myelin-associated markers showed a region-specific divergence: MBP intensity was significantly higher in PPMS rAb-treated spinal cord organoids, but significantly reduced in

PPMS rAb-treated cerebral organoids. SPMS rAbs had no effect on myelin in either organoid type. LFB staining showed similar trends to MBP. Olig2 cell counts were also significantly higher in PPMS rAb-treated spinal cord organoids but not cerebral organoids. These findings confirm the unique pathogenicity of PPMS rAbs and reveal that they exert distinct, region-specific effects on human organoids, impairing neuronal integrity in spinal cord organoids while differentially altering myelin in cerebral vs. spinal cord organoids.

Disclosures: D. Kangriwala: None. **A. Grinberg Mitidieri:** None. **E.T.L. Lynch:** None. **K. Kalpana:** None. **J. Lin:** None. **J.K. Wong:** None. **S.A. Sadiq:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.17/Y17

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch Multiple Sclerosis Research Center of New York (Private Funds)

Title: Region-specific effects of primary progressive and secondary progressive multiple sclerosis CSF on neuronal activity

Authors: *A. GRINBERG MITIDIERI, D. KANGRIWALA, E. T. L. LYNCH, J. LIN, J. K. WONG, S. A. SADIQ;
Tisch MS Res. Ctr. of NY, New York, NY

Abstract: Multiple sclerosis (MS) patients commonly undergo a relapsing-remitting phase of the disease (RRMS) before transitioning into secondary progression (SPMS). However, in primary progressive MS (PPMS), the disease worsens continuously from the onset. While neurodegeneration is known to be a pathological hallmark of progressive MS, it is unclear whether there are mechanistic differences and CNS location-specific effects underlying PPMS and SPMS. In our in vivo model, we previously showed that only PPMS cerebrospinal fluid (CSF) induced disability and axonal damage. Distinct neurotoxic effects were also observed in vitro, with PPMS CSF inducing degeneration of spinal cord neurons whereas SPMS CSF induced cortical neuron degeneration. Thus, our goal was to determine whether PPMS and SPMS CSF affect cortical and spinal cord neuronal activity differently. Rat primary cortical (RCNs) and spinal cord neurons (RSCNs) were cultured in chamber slides or microelectrode array (MEA) plates for 8 and 15 days, respectively. PPMS rAbs were generated from PPMS CSF after isolation of single cells by FACS, PCR sequencing of heavy and light chains, plasmid expression and purification. Primary neurons were treated for 1 day with 50% CSF obtained from all MS subtypes or 10 µg/ml PPMS rAbs. Slide neurons were fixed and stained for Tuj1 for neurite length measurement. Spontaneous neuronal activity was recorded immediately following CSF application, then hourly for 5 hours post-treatment, and at 24 hours. RSCNs had significantly shorter neurites after treatment with PPMS CSF and PPMS rAbs but were

unchanged by SPMS CSF or IgG-depleted PPMS CSF. Conversely, cortical neurite lengths were significantly shorter following SPMS CSF treatment but unaffected by PPMS CSF. Electrophysiology data showed a significant reduction in neuronal spikes for spinal cord neurons after treatment with PPMS CSF, PPMS rAbs and SPMS CSF. On RCNs, MEA recordings after treatment with PPMS CSF revealed a significant increase in the number of spikes, reaching seizure-like activity among several samples. Preliminary data show that IgG-depleted PPMS CSF does not affect RCNs electrical activity, suggesting that the observed influence may be antibody-mediated. SPMS CSF induced a bidirectional modulation of cortical neuronal activity. Overall, we showed that the effects of PPMS and SPMS CSF are distinct and that their impact on neurite length and electrical activity is location-specific. Future studies will aim to confirm whether the effects of PPMS CSF on neuronal activity are antibody-mediated, and to identify the SPMS CSF factors modulating cortical and spinal cord neuronal activity.

Disclosures: A. Grinberg Mitidieri: None. **D. Kangriwala:** None. **E.T.L. Lynch:** None. **J. Lin:** None. **J.K. Wong:** None. **S.A. Sadiq:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.18/Y18

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Tisch Multiple Sclerosis Research Center of New York (private funds)

Title: Reactivity of progressive multiple sclerosis recombinant antibodies in healthy iPSC-derived cerebral and spinal cord organoids

Authors: *E. T. L. LYNCH, D. D. KANGRIWALA, A. GRINBERG MITIDIERI, J. LIN, J. K. WONG, K. KALPANA, S. A. SADIQ;
Tisch Multiple Sclerosis Res. Ctr. of New York, New York, NY

Abstract: Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination within the central nervous system (CNS) and production of oligoclonal bands (OCBs). Identifying the antigenic targets of intrathecal immune cells has remained an area of interest for understanding MS pathogenesis. Cerebral and spinal cord organoids derived from human induced pluripotent stem cells (iPSCs) provide human CNS tissue without the complications associated with endogenous protein binding which can be used to further investigate protein interactions within CNS tissue. CSF samples were obtained from 12 people with MS (PwMS) to produce rAbs: seven with primary progressive MS (PPMS) and five with secondary progressive MS (SPMS). CD138+ and CD19+ single cells were isolated using fluorescence-activated cell sorting (FACS). The immunoglobulin (Ig) variable regions of the heavy and light chains were expressed as full-length IgG1 rAbs. Western blots (WBs) were performed using healthy iPSC-derived cerebral and spinal cord organoid lysates to detect possible antigenic targets. Antibody

reactivity was further assessed using immunofluorescent (IF) staining of human IgG rAb-treated healthy CNS organoids in vitro. Progressive MS rAbs demonstrated reactivity in both healthy iPSC-derived cerebral and spinal cord organoids. WB binding patterns of spinal cord organoid lysate varied, with individual rAbs exhibiting differences in protein binding patterns. PPMS rAbs generally exhibited greater immunoreactivity within spinal cord organoids, consistent with increased human IgG staining observed in PPMS rAb-treated spinal cord organoids. WB analysis of cerebral organoid lysates revealed recurrent immunoreactive protein bands recognized by multiple rAbs. PPMS and SPMS rAbs recognized a protein band at approximately 45 kDa, suggesting the presence of shared antigenic target in healthy iPSC-derived cerebral tissue. The detection of a recurring ~45 kDa protein by multiple MS rAbs supports the presence of shared antigenic target among progressive MS clonally expanded B cells. The reoccurring protein band in healthy cerebral organoids suggest that these rAbs recognize CNS proteins that are not uniquely associated with MS pathology. Ongoing studies in the laboratory are focused on isolating and identifying the protein band to identify potentially relevant antigenic targets in MS.

Disclosures: E.T.L. Lynch: None. **D.D. Kangriwala:** None. **A. Grinberg Mitidieri:** None. **J. Lin:** None. **J.K. Wong:** None. **K. Kalpana:** None. **S.A. Sadiq:** None.

Poster

PSTR054: Translational Studies and Therapeutic Strategies in Multiple Sclerosis

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR054.19/Web Only

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

Title: Effectiveness and Safety of Efgartigimod in Myasthenia Gravis Subtypes: A Meta-Analysis

Authors: *A. ABUHAMDIA[1], H. SABET[2], M. AHMED[2], M. EL-MOSLEMANI[3], D. EWIS[4], Z. ELYAMANY[5], A. KHATATBEH[6], A. ALMARFADI[7], H. RAYESS[8], G. ALTALAB[9], A. ABBAS[10];
[1]Biopsychology and Neuroscience, Collage of Hlth. and Life Sci., Hamad Bin Khalifa Universiy, Doha, Qatar; [2]Fac. of Med., South Valley Univ., Qena, Egypt; [3]Fac. of Med., Al-Azhar Univ., Damietta, Egypt; [4]Fac. of Med., Beni Suef Univ., Beni Suef, Egypt; [5]Fac. of Med., Tanta Univ., Tanta, Egypt; [6]King Hussein Med. Center, Royal Med. Services, Amman, Jordan; [7]Dept. of Med., Ferhat Abbas Univ. of Setif, setif, Algeria; [8]Fac. of Med., Ain Shams Univ., Cairo, Egypt; [9]Fac. of Med., Merit Univ., New Sohag, Egypt; [10]Fac. of Med., Al-Azhar University, Damietta,, Damietta, Egypt

Abstract: Background: Myasthenia gravis (MG) is an acquired autoimmune disorder affecting neuromuscular junction (NMJ) proteins, with a worldwide prevalence of approximately 12.4 cases per 100,000 population. Efgartigimod is a newly engineered Fc fragment of human IgG1, which acts by blocking the neonatal FcRn, reducing IgG and pathogenic antibodies. It has been recently approved for the treatment of MG. Current analyses have addressed short-term response

rates and adverse events in MG patients. Objective: Our meta-analysis aimed to assess changes in the MG Activities of Daily Living (MG-ADL) scale, quantitative MG (QMG) score, and 15-item revised scale for MG of Life (MG-QoL15r), as well as reductions in serum IgG levels and corticosteroid-sparing effects, alongside the long-term response rate and adverse events across MG subtypes. Methods: A comprehensive search was conducted in the PubMed, Scopus, Web of Science, and Cochrane CENTRAL databases until 15 October 2025. Clinical trials and cohort studies evaluating the efficacy and safety of efgartigimod in patients with MG were included. A random-effects model was used to pool the mean differences (MDs) for continuous outcomes and proportions for categorical outcomes, with corresponding 95% confidence intervals (CIs). Subgroup analyses were performed based on the study design and MG subtype. Results: Twenty-nine interventional and observational studies (1594 patients) were included in the analysis. Overall, 83% of patients achieved clinically meaningful improvement (CMI; ≥ 2-point reduction in the MG-ADL score), and 36% achieved minimal symptom expression (MSE; MG-ADL score of 0 or 1) with no significant difference between AChR-Ab-positive and AChR-Ab-negative subtypes. The MG-ADL score significantly decreased from baseline (MD: -4.3 points, 95% CI: -4.99 to -3.61), with no difference between the MG subtypes. QMG score (MD: -3.6 points, 95% CI: -4.28 to -2.91), MG-QoL15r, IgG levels, and corticosteroid use showed significant reductions in the AChR-Ab-positive subtype; however, these outcomes were not observed in the AChR-Ab-negative subtype. Serious adverse events were reported in 4.42% of the patients. Conclusion: Efgartigimod significantly improved clinical symptoms and quality of life in patients with MG and may offer a steroid-sparing effect, with no significant differences observed between the subtypes.

Disclosures: A. AbuHamdia: None. **H. Sabet:** None. **M. Ahmed:** None. **M. El-Moslemani:** None. **D. Ewis:** None. **Z. Elyamany:** None. **A. Khatatbeh:** None. **A. Almarfadi:** None. **H. Rayess:** None. **G. Altalab:** None. **A. Abbas:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.01/Y20

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS126987

Title: Glia, Perineuronal Nets, and Pain Assessment in Developing and Adult Prrxl1 Knockout Mice

Authors: *E. WILLERSON[1,3], G. LI[1,3], J. M. F. LUTCHMAN[3], E. HEKMATI[3], H. LATIFF[4], G. CATALDO[1,3], J. C. BRUMBERG[1,2,3];
[1]Psychology, [2]Biol., The Grad. Center, CUNY, New York, NY; [3]Psychology, [4]Computer Sci., Queens College, CUNY, Flushing, NY

Abstract: Chronic pain will affect upwards of 1-in-5 Americans in their lifetime. This makes finding targets for mitigating chronic pain an imperative area of research. Glia, along with perineuronal nets (PNNs) – lattice-like form of the extracellular matrix that surrounds and stabilizes GABAergic, parvalbumin+ interneurons – are key non-neuronal players in the development and maintenance of chronic pain, making them potential therapeutic targets. Animal models of chronic pain are limited, with most mouse models employing invasive procedures to induce pain (e.g., broken bones), which introduce peripheral tissue damage and experimenter variability. Here, knockout (KO) of Prrxl1 is used to explore the morphology and development of glia and PNNs in chronic pain. Prrxl1 is a homeodomain transcription factor necessary for the development of the brainstem trigeminal nuclei and spinal cord dorsal horn (DH). Prrxl1 KO results in peripheral ganglion neurons having difficulty finding their targets in the DH and trigeminal nuclei. Using von Frey mechanical stimulation, we discovered that KO of Prrxl1 results in concurrent bodily hypoalgesia and orofacial hyperalgesia. Further, we performed morphological reconstructions of microglia in the trigeminal's Principal Sensory Nucleus (PrV), the Spinal Trigeminal Nucleus (SpV), and in the lumbar spinal cord DH. Immunohistochemical staining using Ionized Calcium Binding Adapter Molecule 1 (IBA-1) was performed to reveal microglia. Measures of microglial complexity (number of nodes, branches, soma size, branch length) were compared between nuclei, mouse strain, age, and sex. Microglia in both the PrV and SpV of adult Prrxl1 KO mice show significant reduction in complexity compared with WT mice. PNNs were stained using wisteria floribunda agglutinin (WFA). Density was assessed via luminance (average brightness per pixel when imaged using light microscopy), and found to be significantly reduced in the PrV of adult Prrxl1 KO mice when compared with WT counterparts. We further assessed the development of chronic pain and changes to glia across early development (P3-P30) of Prrxl1 mice. We found that Prrxl1 KO causes significant sensitization to von Frey monofilaments presented in early life (P3) which reduces in the first two weeks of life, before sensitizing again towards adulthood (P21). Microglia, PNNs, and astrocytes were similarly assessed. Our results point to the Prrxl1 KO mouse as a useful model for studying chronic pain and its non-neuronal components.

Disclosures: E. Willerson: None. **G. Li:** None. **J.M.F. Lutchman:** None. **E. hekmati:** None. **H. Latiff:** None. **G. Cataldo:** None. **J.C. Brumberg:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.02/Y21

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5SC3GM122657

Title: Attenuation of Cold Allodynia as Evidence of Trigeminal Neuropathic Pain in Prrxl1 Knockout Mice

Authors: *J. VACCARO[1], J. C. BRUMBERG[2], G. CATALDO[3];
[1]Queens College, City Univ. of New York (CUNY), Flushing, NY; [2]CUNY Grad. Ctr., New York, NY; [3]Queens College. CUNY, Flushing, NY

Abstract: Cold allodynia, where normally innocuous cooling is experienced as pain, stands as a prominent feature of neuropathic pain affecting as many as 50% of patients and up to 90% of those taking certain common platinum-based chemotherapies. Prrxl1, a homeodomain transcription factor, is indispensable for development of the trigeminal pathway. Its deletion disrupts patterning of primary sensory afferents from the whisker to barrel cortex originating at the mystacial pad. Deletion of Prrxl1 in mice is also associated with hyperalgesia to stimulation of the orofacial region and taken together, we used Prrxl1 knockout (KO) mice as a model of trigeminal neuropathic pain. We hypothesized that these facially mechanically hyperalgesic mice would additionally have a heightened response to cooling which would be attenuated by gabapentin. In order to measure cold allodynia, we utilized the Peltier effect via a thermoelectric cooler. We applied one side of the cooler onto the face/mystacial pad of the mice. By doing so, we were able to identify the temperature at which they exhibited a withdrawal response to application of cold, thereby signaling sensitivity to cooling. Results showed that facial withdrawal responses of Prrxl1 KO mice were greater than those of control animals, which did not respond to cooling of the mystacial pad from approximately 30 degrees Celsius down to 5 degrees. Prrxl1 KOs withdrew at temperatures that were significantly less cold (~14.7 degrees Celsius), suggesting that Prrxl1 mice expressed trigeminal thermal hyperalgesia. We then administered gabapentin, a drug used to treat neuropathic pain. We tested at baseline, 1 hour, 2 hours, and then 3 hours after gabapentin administration and found that Prrxl1 KOs expressed cold allodynia in the orofacial region at baseline. At 1 hour and 2 hours post gabapentin, Prrxl1 KOs did not respond down to 5 degrees Celsius, which mirrored the response of control mice. This suggested that gabapentin effectively treated the neuropathic facial pain. At 3 hours, Prrxl1 KOs began to demonstrate baseline responses to cooling, since the effect of gabapentin diminished by this time. These results, along with previous findings, further support Prrxl1 KO mice as a novel non-invasive model of trigeminal neuropathic pain.

Disclosures: J. Vaccaro: None. **J.C. Brumberg:** None. **G. Cataldo:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.03/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Support: Queens College Research Enhancement Grant
Transfer for STEM Student Success program, CUNY, supported by the Alfred P. Sloan Foundation

Title: Quantifying Grooming in a Mouse Model of Trigeminal and Somatic Neuropathy

Authors: *G. LI[1], H. LATIFF[2], J. C. BRUMBERG[2], G. CATALDO[2];
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[2]Psychology, Queens College, The City Univ. of New York, Flushing, NY

Abstract: Paired related homeobox protein like 1 knockout (Prrxl1-KO, also known as Drg11-KO) mice are a candidate model of neuropathic orofacial pain, exhibiting aberrant grooming and self-injury behaviors that may reflect chronic discomfort. Prrxl1-KO mice lack somatotopic organization in the barrel cortex and barrelettes, along with extensive neuropathy in the principal sensory trigeminal nucleus and aberrant peripheral connectivity, leading to facial hyperalgesia and rear body hypoalgesia, with frequent skin lesions in both regions. As forepaw wiping and manipulation of irritated areas are expressions of pain, we suggest that this aberrant grooming, an extension of wiping behavior, is a potential measure of pain. Carprofen, a common non-steroidal anti-inflammatory analgesic, did not alter grooming behavior in novel open field measures but revealed that Prrxl1-KO mice showed aberrant grooming when compared to wild type mice, suggesting these mice experienced neuropathic and not peripheral nociception and a suppressive effect of anxiety. Gabapentin, which acts on voltage-gated calcium channels to inhibit excitatory neurotransmission and treats neuropathic pain, did not alter Prrxl1-KO grooming in home cage environments, suggesting grooming duration may not be a direct indicator of neuropathic pain. We further analyzed the aberrant grooming behavior, showing differences in grooming by location and that Prrxl1-KO mice injury presentation in the rear correlates with grooming time, suggesting that hypoalgesia in the rear is a potential driver of aberrant grooming. These data, taken together, suggest that grooming may not be a direct measure of pain, but components may reflect aspects of hyperalgesia and hypoalgesia, as grooming remains aberrant and more frequent when compared to wild types. As well, we show the viability of quantifying complex behaviors and behavior components through machine learning techniques to extend research toolkits for establishing measures in mice.

Disclosures: G. Li: None. **H. Latiff:** None. **J.C. Brumberg:** None. **G. Cataldo:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.04/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Title: The combination of social isolation model plus cuprizone administration induce anxiety-like behavior and hyperalgesia in female adult CD1 mice

Authors: T. V. CAMPOS ORDONEZ[1], B. ORTEGA-VALLES[1], G. GUDIÑO-CABRERA[1], J. PEREGRINA-SANDOVAL[1], ***E. LIRA**[2,1];
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[2]Dept. de Biología Celular y Mol., Univ. de Guadalajara, Zapopan, Mexico

Abstract: Background: the stress is an alteration of the homeostatic equilibrium triggered by physic and psychologic factors. Thus, the stress could by acute and chronic depending of the stimuli duration. Since the acute stress is transitory, the chronic stress is associated with maladaptive alterations like depression, anxiety and inflammation. The animal models are useful for the study of the anxiety; however, the animals show a wide behavioral spectrum. In this regard, the combination of animal models like social isolation (stress/anxiety) and cuprizone (demyelination and neuroinflammation) to obtain behavioral features similar to those shown by humans, could comprehensively represent a useful model to study the behaviors associated with anxiety. Objective: to evaluate anxiety-like behavior and hyperalgesia in CD1 mice after social isolation and parallel administration of cuprizone 0.5%. Methods: adult (8 weeks) female CD1 mice were socially isolated for four weeks, at the same time were administered with cuprizone 0.5%. As control groups: social and isolated animals with standard chow and, the fourth one was social with cuprizone 0.5%. For the behavioral analysis we perform the open field test and elevated plus maze and von Frey test (hyperalgesia). Results: our results show that social isolation plus cuprizone increase the exploratory behavior (movement, distance traveled and climbing), also hyperalgesia was observed. Conclusion: the social isolation and cuprizone increased the anxiety-like behaviors and hyperalgesia.

Disclosures: T.V. Campos Ordonez: None. **B. Ortega-Valles:** None. **G. Gudiño-Cabrera:** None. **J. Peregrina-Sandoval:** None. **E. Lira:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.05/Y23

Topic: E.01. Somatosensation – Pain and Itch

Support: SECIHTI Grant CBF-2025-I-3397

Title: Prenatal exposure to experimental preeclampsia induces sex-specific alterations in peripheral nociception in adult offspring

Authors: *C. E. ELIZONDO-MARTINEZ, A. L. LAGUNES-SANTIAGO, A. D. HERNANDEZ-MARTINEZ, E. K. VASQUEZ-CRUZ, R. I. ACOSTA-GONZÁLEZ, A. MARTÍNEZ-MARTÍNEZ, J. JIMENEZ-ANDRADE, E. MUÑOZ-ISLAS;
Unidad Académica Multidisciplinaria Reynosa-Aztlán, Univ. Autónoma de Tamaulipas, Reynosa, Mexico

Abstract: Preeclampsia (PE), an obstetric multisystemic syndrome, is a leading cause of maternal and perinatal mortality worldwide, profoundly impacting fetal and postnatal development. While clinical and preclinical studies show that in utero PE exposure is associated with cognitive impairments, such as deficits in spatial learning and working memory, as well as neuronal loss and astrogliosis, the long-term impact on offspring pain neurotransmission remains

unexplored. Thus, this study aims to determine how PE exposure modulates mechanical sensitivity and acute nociceptive behaviors in adult offspring, thereby establishing a behavioral framework to correlate functional responses with histopathological alterations in the skin. To model PE, pregnant mice received L-NAME (50 mg/kg, s.c.) or saline on gestation days (GD) 7.5-17.5. Maternal systolic blood pressure (SBP) and proteinuria were monitored at GD14.5 and 17.5. The body weights of male and female offspring were tracked weekly. Mechanical sensitivity was assessed at postnatal weeks 9-15 using von Frey filaments, followed by evaluation of capsaicin-induced (0.1%, i.pl.) nociceptive behaviors at week 16. Finally, nerve fiber density (PGP-9.5 and CGRP), blood vessels, and macrophage infiltration in glabrous skin are being evaluated via immunohistochemistry (IHC) and confocal microscopy to correlate structural and behavioral changes. Maternal L-NAME administration successfully induced a PE-like phenotype, evidenced by elevated SBP and proteinuria during late gestation. While offspring body weight remained consistent across groups, prenatal PE exposure induced distinct long-term nociceptive alterations. Adult offspring from preeclamptic mothers exhibited baseline mechanical hypersensitivity, showing a decreased 50% withdrawal threshold from weeks 9 to 15, regardless of sex. Interestingly, chemical challenges revealed sex-specific vulnerabilities: PE-exposed female offspring displayed a marked exacerbation in acute pain behaviors, characterized by a significant increase in both the number of capsaicin-induced flinches and guarding time compared to all other groups. Furthermore, histopathological evaluations of the epidermis and peripheral inflammatory cell infiltration are underway to elucidate the underlying structural mechanisms. Prenatal exposure to PE induces mechanical hypersensitivity and alters acute nociceptive responses in adult offspring, with pronounced sex differences. Ongoing IHC analyses will determine whether these functional alterations correlate with localized structural changes in the vasculature, immune system, or peripheral nerves.

Disclosures: C.E. Elizondo-Martinez: None. **A.L. Lagunes-Santiago:** None. **A.D. Hernandez-Martinez:** None. **E.K. Vasquez-Cruz:** None. **R.I. Acosta-González:** None. **A. Martínez-Martínez:** None. **J. Jimenez-Andrade:** None. **E. Muñoz-Islas:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.06/Y24

Topic: E.01. Somatosensation – Pain and Itch

Title: Glucocorticoid and mineralocorticoid receptor antagonists prevent postoperative opioid withdrawal-induced hyperalgesia following acute fentanyl exposure

Authors: *M. JOHNSTON[1,2], C. O'BRIEN[2,1], J. VENDRUSCOLO[2,1], L. F. VENDRUSCOLO[3,1];
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Abstract: Opioids are widely used in surgical settings for the maintenance of anesthesia and for postoperative pain management. Paradoxically, the use of opioids poses a risk for the development of postoperative hyperalgesia, or heightened pain sensitivity. Mechanistically, chronic opioid exposure dysregulates major stress-response systems in the body, including the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) signaling. Specifically, GR and MR antagonists have been observed to reverse opioid withdrawal-induced hyperalgesia and decrease opioid consumption. Therefore, we hypothesize that GR and MR antagonists used as an adjuvant to anesthesia could attenuate the subsequent development of hyperalgesia. To test our hypothesis, male Long-Evans rats were pre-treated with either the GR antagonist mifepristone, the MR antagonist spironolactone, or the GR/MR antagonist miricorilant, then anesthetized with isoflurane and administered a continuous intravenous infusion of fentanyl for one hour. Rats were then tested for mechanical sensitivity at three different time points to examine the development of hyperalgesia. We observed that rats exposed to fentanyl exhibited a robust analgesia 1 h after recovery from anesthesia. However, they showed pronounced hyperalgesia at 24 h. Mifepristone, spironolactone, and miricorilant all prevented the development of hyperalgesia without affecting analgesia. Future work will test females and examine the role of central versus peripheral sensitization in the development of hyperalgesia.

Disclosures: M. Johnston: None. **C. O'Brien:** None. **J. Vendruscolo:** None. **L.F. Vendruscolo:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.07/Y25

Topic: E.01. Somatosensation – Pain and Itch

Support: T32 DE014318/DE/NIDCR NIH HHS/United States

Title: Peripheral Recombinant LIGHT (TNFSF14) Inhibits Oral Cancer Pain by Modulating the Immune Response

Authors: *J. N. MERLO[1], T. IBRAHIM[1], S. SHEIN[1], A. TUMANOV[1], S. RUPAREL[2]; [1]Univ. of Texas Hlth. Sci. Center, San Antonio, San Antonio, TX; [2]Endodontics, Univ. of Texas Hlth. Sci. Ctr. At San Antonio, San antonio, TX

Abstract: Head and neck cancer (HNC) is the sixth most common malignancy globally, accounting for approximately 890,000 new cases and 450,000 deaths each year. Alarmingly, the incidence of HNC continues to rise and is projected to increase by 30%, reaching an estimated 1.08 million cases annually by 2030. 50-85% of HNC patients report pain from oral squamous cell carcinomas (OSCC), as the most prominent and distressing symptom driving patients to seek clinical care. The pain is often severe and localized to the primary tumor site, even when the

tumor is small, and can manifest as spontaneous pain, referred pain throughout the orofacial region, and impairment of vital functions such as speech, swallowing, and mastication. Most oral cancer patients require opiates, however, OSCC patients frequently experience long-term adverse effects associated with these treatments. Patients exhibit one of the highest opioid re-escalation indices, indicating rapid tolerance development and highlighting the urgent need for improved pain management strategies. Our lab identified a novel target, LIGHT (or TNFSF14), that possesses an immunomodulatory role in several inflammatory and autoimmune diseases. This soluble ligand has two receptors: Lymphotoxin-beta (LTβR) and HVEM. This study tested the contribution of LIGHT in oral cancer pain. We used a mouse orthotopic tongue cancer pain model and locally injected recombinant LIGHT (rLIGHT) to assess the effects on oral cancer pain behaviors. Additionally, we tested the expression of LIGHT receptors in normal and tumor-bearing tongues of mice using RT-PCR and IHC. Expression of receptors was confirmed in human tongue tumor biopsies. We evaluated the contribution of the immune system in mediating rLIGHT effects using flow cytometry. Local injection of rLIGHT into the tongue reversed oral cancer pain behaviors including feeding behavior and mechanical hypersensitivity in the face. RT-PCR expression of LIGHT receptors showed expression of LTβR and HVEM in tumor-bearing tongues compared to normal; of which LTβR was significantly robust in expression compared to HVEM. Cell source of LTβR revealed strong expression in cancer cells of the mouse model and human tumor biopsies. rLIGHT also caused an increased macrophage population in the tongue, indicating a possible role of the innate immune system in mediating rLIGHT effects on oral cancer pain. Collectively our data indicates that LIGHT may be a novel target in inhibiting oral cancer pain, producing its effect via its receptor LTβR, possibly modulating the local immune response in tumor-bearing animals.

Disclosures: J.N. Merlo: None. **T. Ibrahim:** None. **S. Shein:** None. **A. Tumanov:** None. **S. Ruparel:** None.

Poster

PSTR055: Pain Models

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.08/Y26

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant NS065326
NIH HEAL Initiative U19NS130608

Title: Chemotherapy-induced impairment of lysosomal motility in human DRG neurons

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Abstract: Dorsal root ganglion (DRG) neurons have extremely long axons and high metabolic demands. Maintaining homeostasis requires optimal lysosomal function and integrity, which coordinate the synthesis of macromolecules and the degradation of damaged organelles. Previous studies have identified lysosomes as stress response coordinators, nutrient sensors, and part of critical signal transduction hubs. Lysosome dysfunction has been linked to various lysosomal storage disorders, which cause pathological changes in the axons of DRG neurons. However, there is limited information on how axonal lysosomes function following chemotherapeutic treatment in human DRG neurons. Since DRG neurons lack a blood-nerve barrier, they are highly permeable to chemotherapeutic agents, resulting in toxicity and axonal degeneration, which can lead to peripheral neuropathy—a dose-limiting side effect of chemotherapy that may last long-term. With cancer survival rates improving remarkably, mitigating chemotherapy-induced peripheral neuropathy (CIPN) has become a pressing need. In our earlier findings, we demonstrated that lysosomal motility is significantly decreased in the soma of PTX-treated mouse DRG neurons. Therefore, this current study aims to determine the effects of the chemotherapeutic agents paclitaxel (PTX) and vincristine (VCN) on lysosomal trafficking in the axons of primary human DRG neurons. Additionally, since our previous work showed heightened MNK1/2-eIF4E signaling in DRG neurons after PTX treatment, we examined whether MNK1/2 inhibition using Tomivosertib (eFT508), a potent MNK1/2 inhibitor, could also restore lysosomal function. Using Lysotracker to stain lysosomes and a spinning disk super-resolution microscope (SPINSR) for live cell imaging, we observed that PTX and VCN treatments, respectively, decrease lysosomal speed in the axons of hDRG neurons, and that concurrent administration of eFT508 increases their speed. We further show that human DRG neurons treated with PTX or VCN exhibit heightened phosphorylated eIF4E, and concurrent administration with eFT508 attenuates this effect. Taken together, these findings suggest that PTX and VCN, despite their different mechanisms of action, disrupt lysosomal trafficking, and that MNK inhibition with eFT508 increases lysosomal motility and can play a neuroprotective role for CIPN.

Disclosures: K. Domalogdog: None. **S. Nguyen:** None. **Ú. Franco-Enzástiga:** None. **I. Sankaranarayanan:** None. **T.J. Price:** None.

Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: 4-VA Collaborative Research Grant
NIH 5R21CA296516

Title: Proteomic Adaptations in the Spinal Cord and Dorsal Root Ganglia of a Breast Cancer Model of Paclitaxel-Induced Peripheral Neuropathy

Authors: *S. P. SCHWARTING[1], V. ESPINA[2], P. RUSSO[2], S. HERZ[3], A. KHAN[3], Y. RAKHOLIA[3], S. MAKAR[4], C. LOCKHART[1], P. BOS[4], M. DAMAJ[3], N. KABBANI[1];
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating and dose-limiting side effect of taxane-based chemotherapy used to treat several cancers, including breast cancer. Despite its prevalence, no FDA-approved therapies currently exist for the prevention or treatment of CIPN, highlighting the need to identify novel therapeutic targets. Using liquid chromatography-electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS), we examined the acute effects of paclitaxel (8 mg/kg every other day for 4 doses) on proteomic profiles in the L4-L6 spinal cord and dorsal root ganglia (DRG) of MMTV-PyMT-derived breast tumor-bearing mice 7 days after the first injection. Paclitaxel treatment reduced tumor size and intra-epidermal nerve fiber (IENF) density in tumor-bearing mice, consistent with established antitumor efficacy and paclitaxel-induced IENF loss or reduction. Proteomic analysis revealed significant alterations in both spinal cord and DRG protein expression following paclitaxel treatment and identified distinct proteomic signatures associated with breast cancer. Moreover, comparison of proteomic changes between paclitaxel-treated tumor-bearing and non-tumor-bearing mice suggested a potential role for cancer in shaping sensory tissue responses to paclitaxel. Gene ontology enrichment and STRING network analyses identified pathways related to mitochondrial metabolism, ion transport, and neurotransmitter signaling. Collectively, these findings define proteomic alterations induced by paclitaxel in the spinal cord and DRG and suggest that cancer-specific mechanisms may contribute to the development of CIPN, providing potential targets for future therapeutic intervention.

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Poster

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Program #/Poster #: PSTR055.10/Y28

Topic: E.01. Somatosensation – Pain and Itch

Title: Tracking Locus Coeruleus Activity in the Oxaliplatin-induced CIPN Mouse Model

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Abstract: Almost 80% of patients receiving oxaliplatin to treat colorectal cancer develop persistent chemotherapy-induced peripheral neuropathy (CIPN) symptoms (Park et al., 2011; Teng et al., 2022). The toxic DNA-damaging effects of oxaliplatin are enriched in primary sensory neurons (Devanabanda & Kasi, 2026), creating a peripheral polyneuropathy. Naturally, CIPN research has been focused on the peripheral nervous system, leaving the impacts of CIPN on the central nervous system (CNS) understudied. In surgically induced models of mononeuropathy, namely chronic constriction injury (CCI), spared nerve injury (SNI), and spinal nerve ligation (SNL), there is evidence that the locus coeruleus becomes tonically active after injury. Interestingly, in states of tonic LC activation, some studies have reported reduced spinal norepinephrine (NE) release (Saito et al., 2015). Here, to ask whether tonic LC activity and reduced spinal NE are also observed in a CIPN model, we performed immunohistochemistry for c-Fos in the LC to measure activity and for dopamine beta-hydroxylase (DβH) to measure NE content in the dorsal horn of the spinal cord. C57BL/6J male mice were injected with oxaliplatin intraperitoneally for a total of 10 doses, which causes cumulative damage to sensory neurons, and were perfused at 1, 2, 4, and 6 weeks after oxaliplatin dosing. We also explored whether spinal cord dorsal horn α2-adrenergic receptors (α2ARs), which provide antinociception when stimulated, are differentially regulated over time after oxaliplatin. This study extends findings of circuit-specific neuropathic pain mechanisms to CIPN and may identify differences in these disease models that carry clinical relevance.

Disclosures: J. Vaughn: None. **V. Brings:** None. **A.J. Crowther:** None.

Poster

PSTR055: Pain Models

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Program #/Poster #: PSTR055.11/Y29

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant CA241627
NIH Grant CA263777

Title: Contribution of spinal HIF-1α - COX-2 signaling to bone cancer-induced pain

Authors: *L. M. NEAL[1,2], I. A. KHASABOVA[2], X. ZHANG[2], M. JOHNS[2], R. MOHAMMED[2], A. G. HAGSTRÖM[2], K. BRAUN[2], V. VIATCHENKO-KARPINSKI[2], D. A. SIMONE[2], S. G. KHASABOV[2];
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Abstract: Pain from primary or metastatic bone tumors is one of the most severe and difficult conditions in oncology. Hypoxia, low oxygen levels, is an important factor underlying the growth and metastasis of bone tumors. However, there is insufficient evidence to support its effect on induced and spontaneous bone tumor-related pain. Here, we investigated the

contribution of hypoxia-inducible factor-1α (HIF-1α), the main transcriptional marker of hypoxia, to mechanical hyperalgesia and spontaneous pain in a mouse model of bone cancer, in which fibrosarcoma cells were implanted in and around the calcaneus bone. Tumor growth produced mechanical hyperalgesia, defined as a decrease in paw withdrawal threshold, and spontaneous pain, which was monitored using the Blackbox BB1 system. Importantly, pain was accompanied by a simultaneous increase in the expression of HIF-1α and COX-2 mRNA, as well as the level of PGE2 in the spinal cord. The regulation of COX-2 by HIF-1α was confirmed through suppressing HIF-1α via intrathecal administration of HIF-1α siRNA. This reduced COX-2 expression in the spinal cord, which led to a decrease in mechanical hyperalgesia in tumor-bearing mice. Moreover, intrathecal administration of 1,4-DPCA, an HIF-1α stabilizer, increased the expression of COX-2 and produced mechanical hyperalgesia and spontaneous pain in naïve mice. Electrophysiological studies showed that HIF-1α stabilization also induced sensitization of WDR neurons in the spinal cord, defined as an increase in spontaneous activity, lowering the mechanical response threshold, and increasing responses to suprathreshold mechanical stimuli. Our results show that increased expression of HIF-1α contributes to the development of mechanical hyperalgesia and spontaneous pain in a mouse model of bone cancer by activating COX-2 signaling. Thus, HIF-1α inhibition may represent a new approach to treating bone cancer pain.

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Poster

PSTR055: Pain Models

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Topic: E.01. Somatosensation – Pain and Itch

Support: National Institutes of Health grant NS117340
National Institutes of Health grant NS094438
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Title: IgG Autoantibody Signaling through Fc Receptors in Osteoarthritic Pain Murine Models

Authors: *P. SAHBAIE[1], X. SHI[2], T.-Z. GUO[3], S. SANAEI ESFAHANI[4], W. KINGERY[5], D. CLARK[2];
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Abstract: Pain is the sentinel symptom of osteoarthritis (OA) and is a key driver of medical care utilization. The mechanisms of OA-related pain are poorly described while analgesic therapy is non-specific and of limited efficacy. Accumulating evidence suggests that autoantibodies against joint proteins are formed in the setting of OA and potentially contribute to inflammation, joint degeneration and pain. We hypothesized that a recombinant IgG1-Fc hexamer acting as Fcγ-receptor (FcγR) antagonist would reduce the pain-related behaviors in murine models of OA. These studies used both the monoiodoacetate (MIA) and disruption of the medial meniscus (DMM) models of OA in male C57BL/6 mice. Additional experiments used Fcer1g knockout mice lacking functional stimulatory IgG Fc receptors. Nociceptive sensitization was measured using hind paw von Frey mechanical thresholds, knee joint pressure testing and hindpaw unweighting. Effects of the FcγR blocker Fc-μTP-L309C (CSL777) were measured after systemic and intraarticular administration. Expression levels of the FcγR genes Fcgr1 (CD64), Fcgr2b (CD32b), Fcgr3 (CD16) and Fcgr4 (CD16-2) were measured in lumbar dorsal root ganglia using qPCR. Immunoblotting of tissues from OA joints was used to measure IgG accumulation, and ELISA studies quantified binding activity against pain-related autoantigens. In the MIA model, wild type C57BL/6 mice developed mechanical allodynia, knee joint hyperalgesia and hindpaw unweighting while mice lacking Fcer1g displayed only transient allodynia. In lumbar DRGs several FcγR genes had elevated mRNA levels; Fcgr1 (by >65%; $p = .0011$), Fcgr2b (by >70%; $p < .001$), Fcgr3 (by >70%; $p < .001$) and Fcgr4 (by >30%; $p = .012$) by 4 weeks after MIA injection. IgG had accumulated in the MIA joints, and the IgG binding of candidate autoantigen proteins had increased after MIA injection. Systemic CSL777 administration reduced nociceptive sensitization within 48 hours, allodynia was decreased at 1 (by >60%; $p < .001$) and 4 weeks (by >80%; $p = .011$) after MIA injection. Experiments performed on DMM mice also revealed analgesic effects of systemic CSL777 injection. Intraarticular injection of CSL777 was without effect on nociceptive sensitization. Nociceptive sensitization in two models of OA could be reduced by the systemic but not local administration of an FcγR blocker in male mice. The development of such blockers to reduce OA-related pain by this novel mechanism may be feasible.

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Poster

PSTR055: Pain Models

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.13/Y31

Topic: E.01. Somatosensation – Pain and Itch

Support: Abbott Grant

Title: Dorsal Root Ganglion Stimulation Reduces Nociceptor Hyperactivity and Pain Behaviors in a Rat Model of Osteoarthritis

Authors: ***S. WU**[1], Y. LIU[2], D. MUELLER[3], T. CHENG[2], H.-J. PARK[4], B. PAN[2];
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Abstract: Osteoarthritis (OA) is a major cause of chronic pain and disability worldwide, yet effective treatments for OA pain remain limited. Neuromodulation targeting the dorsal root ganglion (DRG) has emerged as a promising strategy for chronic pain management, but its effects on osteoarthritis pain and nociceptor activity remain unclear. Here, we examined whether DRG stimulation can alleviate pain behaviors and modulate peripheral sensory neuron activity in a rat model of OA induced by monosodium iodoacetate (MIA). OA was induced by intra-articular MIA injection in rats. Seven days after MIA injection, L3 DRG stimulation was applied continuously for two weeks. Pain-related behaviors were assessed using mechanical sensitivity tests and dynamic weight-bearing analysis (Blackbox). Teased-fiber electrophysiological recordings from dorsal root fibers were performed to measure spontaneous and evoked nociceptor activity. Histological analysis of the knee joint was conducted to evaluate knee pathology. DRG stimulation significantly reduced mechanical hypersensitivity and improved weight-bearing distribution in MIA-OA rats. Teased-fiber recordings further demonstrated that DRG stimulation markedly decreased spontaneous firing of L3 DRG neurons. In contrast, histological analysis revealed no significant differences in cartilage degeneration between stimulated and non-stimulated animals. These findings demonstrate that DRG stimulation alleviates OA pain by suppressing nociceptor hyperactivity, even in the presence of persistent joint damage. The results indicate that DRG stimulation primarily acts through neuromodulation of sensory pathways rather than structural modification of the joint.

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Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.14/Y32

Topic: E.01. Somatosensation – Pain and Itch

Support: Trauma Research and Combat Casualty Care Collaborative - TRC4

Title: Investigating Distinct Pain Phenotypes in Chemical and Surgical Models of Osteoarthritis

Authors: ***D. M. MUELLER**, S. WU, Y. LIU, T. CHENG, B. PAN;
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Abstract: Osteoarthritis (OA) is a prevalent and debilitating joint disease affecting over 600 million people worldwide, yet no disease-modifying therapies are currently available. Preclinical studies commonly employ two rat models of knee OA: the monosodium iodoacetate (MIA) chemical model and the anterior cruciate ligament with medial meniscal transection (ACLT-MMx) surgical model, which induces joint instability. However, these models often produce discordant behavioral outcomes, raising questions about their translational relevance. We hypothesize that these discrepancies reflect distinct chemical versus mechanical phenotypes of OA pain rather than experimental inconsistency. Pain-related behaviors were longitudinally characterized in MIA and ACLT-MMx OA models. Mechanical sensitivity was assessed using von Frey and pin-prick tests. Joint-associated pain was evaluated using dynamic weight-bearing analysis, and movement-evoked pain was examined using a knee mobilization challenge. Knee histology was performed to assess joint pathology. Teased-fiber electrophysiological recordings were conducted to measure spontaneous activity of dorsal root fibers innervating the knee. Distinct phenotypes were observed in the two models. In the MIA model, there was an early onset of allodynia and hyperalgesia, whereas the ACLT-MMx model showed a reduction in von Frey threshold 3-4 weeks after surgery and a delayed onset of pinprick hyperalgesia. Dynamic weight-bearing analysis revealed clear weight-bearing asymmetry in MIA-treated rats, while ACLT-MMx rats exhibited minimal asymmetry that became apparent only after a knee mobilization challenge. Intra-articular injection of lidocaine blocked weight bearing asymmetry after the knee mobilization challenge in PTOA rats. Consistent with these behavioral differences, teased-fiber recordings demonstrated higher spontaneous activity in dorsal root nociceptors from MIA-OA animals compared with ACLT-MMx-OA animals. Histological analysis showed widespread cartilage degradation in the MIA model, with focal cartilage degradation and bone remodeling observed in late-stage PTOA. MIA and ACLT-MMx models exhibit distinct phenotypes with differences in hypersensitivity onset, nociceptor activity, and joint pathology. These findings suggest that chemical and mechanically induced OA models capture different drivers of osteoarthritis pain and represent complementary systems for studying OA pain mechanisms.

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Poster

PSTR055: Pain Models

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.15/Z1

Topic: E.01. Somatosensation – Pain and Itch

Title: Local Field Potential Activity During the Transition Toward Death Following Prior Nociceptive and Electroconvulsive Stimulation

Authors: *D. IBARRA[1], J. TREJO[2], Y. B. PENG[3];
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Abstract: Near-death experiences (NDEs) are often characterized by reports of heightened awareness and vivid sensory experiences during the transition toward death. However, little is known about how prior neural experiences may influence these phenomena. The present study investigated neural activity during CO_2-induced euthanasia in animals with different histories of noxious input and electroconvulsive stimulation (ECS). Local field potentials (LFPs) were recorded from the anterior cingulate cortex (ACC), left and right central amygdala (CeA), and ventral tegmental area (VTA). Animals were assigned to one of three groups: formalin only, formalin followed by ECS, or ECS followed by formalin. After the completion of a separate study, animals underwent the euthanasia process consisting of a 2-minute baseline followed by a brief 1-minute-high anesthesia, 5-minute anesthesia withdrawal, terminating with a single continuous dose of CO_2 exposure. Oscillatory power was analyzed across delta (0.1-3 Hz), theta (3-7 Hz), alpha (7-12 Hz), beta 12-30 Hz), and gamma (30-100 Hz) frequency bands. Following removal of the brief high dose of anesthesia, neural activity heightened across all recorded brain regions. Animals previously exposed to ECS displayed distinct oscillatory patterns compared to formalin-only animals in all four brain regions, at specific frequency bands. Results reveal three minutes after the onset of CO_2 exposure, a brief rebound in oscillatory activity was observed across multiple frequency bands and brain regions. Following the rebound period, neural activity gradually declined across all groups during continued CO_2 exposure. These results suggest that neural activity during the transition toward death is characterized by dynamic changes rather than a simple decline in activity. Additionally, prior exposure to ECS and pain-related stimulation appears to influence terminal oscillatory responses across brain circuits. The rebound in activity observed after CO_2 exposure reflects distinct changes across multiple brain regions as a transition towards death, with electrical brain stimulation revealing possible influences on the dying process.

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Poster

PSTR055: Pain Models

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Topic: E.01. Somatosensation – Pain and Itch

Support: FAPESP. process no. 2025/05717-8
FAPESP. process no. 2022/04387-6

Title: Evaluation of sensitive responses in male and female mice in a reserpine induced fibromyalgia model

Authors: *S. J. CARDENAS[1], M. SANTOS MORENO[1], L. CANTO DE SOUZA[2], R. L. NUNES-DE-SOUZA[3], D. B. SOUZA[4];
[1]Sch. of Pharmaceut. Sciences, São Paulo State University, UNESP, Araraquara, Brazil; [2]Sch. of Pharmaceut. Sci., Sao Paulo State Univ. (UNESP), Araraquara, Brazil; [3]Pharmacol., Sao Paulo State Univ. - UNESP, Araraquara, Brazil; [4]UNESP, Araraquara, Brazil

Abstract: Fibromyalgia (FM) is a complex, chronic pain disorder characterized by a multifaceted interaction of physical, emotional, and social factors (Pinto et al., 2023). Clinical data estimate a substantial global prevalence of FM with a marked gender bias, predominantly affecting women (Cabo-Meseguer, A et al., 2017). Despite well documented sex-dependent differences in the molecular mechanisms underlying pain pathways, preclinical research has historically excluded female subjects, thereby creating a significant translational gap (Mogil, 2016). While the reserpine induced fibromyalgia model has emerged as a valuable tool for investigating FM pathophysiology (Nagakura et al., 2009), protocol consistency across sexes remains to be fully established. This study aimed to standardize a reserpine-induced fibromyalgia protocol to assess sensory and nociceptive components of pain in both male and female mice. Male and female C57BL/6 mice received subcutaneous injections of reserpine (0.5 mg/kg) or saline. Nociceptive behaviors were evaluated via mechanical thresholds using Von Frey monofilaments, alongside the Mouse Grimace Scale (MGS) to monitor spontaneous, non-reflexive pain expressions. Preliminary analysis using a two-way mixed ANOVA with Bonferroni *post-hoc* corrections revealed that mechanical thresholds did not reach statistical significance in either sex at any evaluated time point ($p > 0.05$). However, *post-hoc* analysis of MGS scores in males demonstrated that the reserpine model induced a statistically significant increase in pain manifestations compared to the saline control group across all time points: 1-hour post final injection ($p=0.007$), persisting on Day 4 ($p= 0.005$), and sustained through Day 10 ($p=0.013$). In contrast, female mice exhibited a significant increase in MGS scores only on Day 10 ($p = 0.032$), showing a mere statistical trend 1-hour post injection ($p=0.096$). For both sexes, baseline assessments confirmed complete homogeneity between experimental groups prior to treatment. In conclusion, these preliminary findings underscore a distinct sexual dimorphism within the reserpine induced model, as evidenced by disparate temporal patterns in spontaneous pain expression between sexes. This variability highlights the critical necessity of validating and standardizing preclinical protocols specifically for female cohorts, ensuring that sex-specific trajectories of pain are accurately captured to improve translational outcomes in fibromyalgia research.

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Poster

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Program #/Poster #: PSTR055.17/Z3

Topic: E.01. Somatosensation – Pain and Itch

Support: R01 EY033291
U01 EY034681
T32 EY007035

Title: A novel semi-mobile mouse behavioral assay for quantifying corneal sensation and ocular hypersensitivity in Dry Eye Disease

Authors: *K. E. T. LAISE[1], T. CANNONIER[2], W. LUO[2], V. LEE[1];
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Abstract: The cornea is the most densely innervated tissue in the body. Originating from the ophthalmic division (V1) of the trigeminal ganglion, corneal sensory afferents are heterogeneous, comprising polymodal nociceptors, mechanoreceptors, and cold thermoreceptors. Dry Eye Disease (DED) is a prevalent chronic ocular condition in which in vivo confocal microscopy has revealed corneal nerve loss and aberrant morphology. DED patients report both hypersensitivity and hyposensitivity, suggesting afferents undergo distinct forms of plasticity as the disease progresses. To understand normal ocular sensation and alternations in DED, we established a novel semi-mobile behavioral assay so we can reliably quantify evoked behavioral responses in control mice and a murine DED model using.Twelve male and twelve female 4-8-week-old C57BL/6J mice were included. The hindlimbs and caudal trunk were gently restrained while the head, thoracic trunk, and forelimbs remained unrestrained. Stimuli targeting specific nerve populations were applied: capsaicin (polymodal nociceptors); von Frey Hair (mechanoreceptors); menthol eye drops (cold thermoreceptors); hypertonic saline (acute dryness) and vehicle (control). Blink rate, squinting, and wiping were recorded via webcam imaging and quantified using DeepLabCut. Following baseline recordings, mice underwent lacrimal gland excision to induce DED and were re-recorded at 4- and 8-weeks post-surgery.Mice were quiescent throughout, enabling high-fidelity recordings of evoked responses. DED mice showed altered sensory responses relative to baseline, corresponding with changes in innervation density and projection patterns across afferent subpopulations identified via genetic labeling and immunostaining. No sex differences were observed. The present findings have significant scientific and clinical implications. Conventional tracking systems are ill-suited for corneal responses, requiring cumbersome multi-mirror setups, head fixation, or suspension, the latter two inducing stress and pain. Our paradigm overcomes these limitations. Despite high DED prevalence and rising incidence, no targeted treatments exist. Identifying which corneal nerve populations are most affected enables precise therapeutic targeting. Sex-based comparisons are also clinically relevant, as DED disproportionately affects women. Further studies that correlate morphological, molecular, and functional changes with behavioral responses will elucidate the neurogenic contributions to DED and inform future therapeutics.

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Poster

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Program #/Poster #: PSTR055.18/Z4

Topic: E.01. Somatosensation – Pain and Itch

Title: Neurobiological Markers of Neuropathic Pain in the Peripheral and Central Nervous Systems After Chronic Rotator Cuff Injury

Authors: *A. YOUN[1], J. WEINRICH[2];
[1]Orthopaedic Surgery, Univ. of California, San Francisco, San Francisco, CA; [2]Anesthesia and Perioperative Care, UCSF, San Francisco, CA

Abstract: INTRODUCTION: Chronic pain after rotator cuff injury (RCI) remains inadequately treated. Up to 30% of rotator cuff tear patients require long-term opioid therapy, including many who were opioid-naïve before surgery. These findings suggest that current treatments may not address all pain mechanisms. We therefore investigated the contribution of neuropathic pain to chronic RCI using a murine model.**METHODS:** Male 10-12-week-old C57BL/6 mice underwent rotator cuff injury consisting of supraspinatus and infraspinatus tendon transection with suprascapular denervation (TT+DN; N=6/group). Model validation included assessment of forelimb function using a string-pulling assay and pain using forelimb weightbearing (Blackbox R4). In a separate cohort (N=3/group), cervical spinal cord and bilateral cervical dorsal root ganglia (DRG) were harvested 6 weeks after injury and stained for ATF3, Iba1, and c-FOS. In a third experiment, mice 10 weeks post-injury (N=7) received intraperitoneal gabapentin (30 mg/kg). Isolated forelimb grip strength was measured before and after treatment. Data are reported as mean difference ± SEM; significance was set at $p<0.05$.**RESULTS:** At 10 weeks, TT+DN mice demonstrated impaired string-pulling reaching motion compared with naïve controls (-56.93 ± 14.50, $p<0.01$). Injured mice also showed reduced forelimb weightbearing ratio (-0.41 ± 0.11, $p<0.01$), indicating offloading of the injured limb. Immunofluorescence revealed increased ATF3 and Iba1 expression in cervical DRGs and elevated Iba1 and c-FOS in the cervical spinal cord, consistent with peripheral and central neuronal injury. Gabapentin significantly improved forelimb grip strength ratio relative to baseline (0.30 ± 0.06, $p<0.001$).**DISCUSSION:** We validated a chronic RCI model that produces persistent functional deficits and chronic pain. Injured mice exhibited evidence of neuronal injury in the peripheral and central nervous systems, supporting a neuropathic component to RCI-associated pain. Improvement following gabapentin further implicates neuropathic mechanisms.

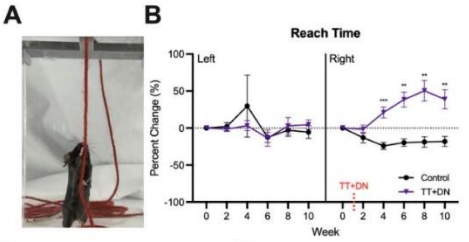


Figure 1. (A) Live image of string-pulling assay. (B) Percent change from baseline of left and right reach time. (C) Representative paw heatmap of bilateral paws in the injured (ipsilateral) and uninjured (contralateral) forelimbs, with increased red/orange indicating more weightbearing. (D) Forepaw weightbearing ratio at 10 weeks post-TT+DN.

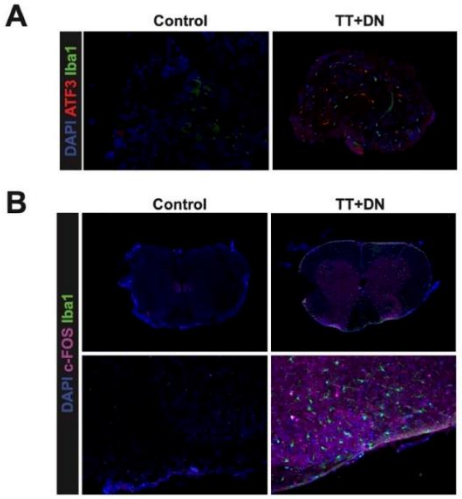


Figure 2. (A) Immunofluorescent images of cervical DRG sections from control and TT+DN mice showing elevated signs of neuronal injury (ATF3, Iba1) in the TT+DN cohort. (B) Immunofluorescent images of cervical spinal cord at 4x and 20x showing elevated signs of neuronal injury (c-FOS, Iba1) in the TT+DN cohort.

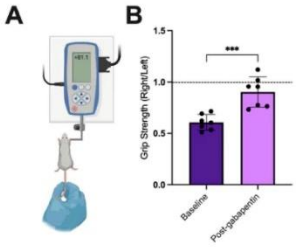


Figure 3. (A) Depiction of isolated forelimb grip strength assay. (B) Grip strength (right/left) at baseline and post-gabapentin administration.

Disclosures: A. Youn: None. **J. Weinrich:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.19/Z5

Topic: E.01. Somatosensation – Pain and Itch

Support: NSF SBIR AWARD# 2516905

Title: Validating a new tool for automating and analyzing somatosensory assays across paw and visceral pain models and analgesics in mice.

Authors: *J. BURDGE[1], I. ABDUS-SABOOR[2], J. K. THACKRAY[3];
[1]Tactorum Inc, New York, NY; [2]Biol., Columbia Univ., NEW YORK, NY; [3]Rutgers Univ., New Brusnwick, NJ

Abstract: To meet the burden posed by chronic pain, researchers have worked to identify potential analgesics using rodent and other animal models, but these have failed to translate into new analgesics for patients. A potential cause of this translational dearth is the outdated techniques used to measure pain in rodents, which often yield limited analytical outputs and introduce extensive experimental confounds due to experimenter error, bias, and variation. This problem is especially prevalent in the common variety of pain assays, high-throughput evoked assays. We have developed the ARM (automated reproducible mechano-stimulator) system and shown that it eliminates error, bias, and confounds introduced by the researcher's presence in evoked pain assays. Further development of the device has allowed for the measurement of a range of behavioral features (Burdge, 2025), including both automated measures of mechanical sensitivity (withdrawal latency, mechanical threshold) and more complex measures of the behavioral response (paw max height, velocity, distance traveled, grimace, shaking, and guarding). To further validate the device and compare it against von Frey testing for both the paw and visceral targets, we tested both across commonly used mouse models of pain, including the spared nerve injury neuropathic pain model, paclitaxel chemotherapy-induced sensitivity model, and the Cyclophosphamide bladder pain model. Each of these groups will be tested at baseline, post-induction, and analgesic timepoints, using up-down von Frey testing and 0.5 g and 1.5 g stimulus testing from the ARM. They will be compared for efficacy, variability, and experimental time across timepoints. To further improve the ARM's consistency and remove experimenter influence, a new automated aiming strategy will be used, with a live pose analysis model tracking points across the mouse head, tail, and fore and hind paws, which will be analyzed in real time to identify the desired target and ensure ideal stimulus conditions. Finally, a new thermal stimulus module for the device using a heated filament applied by the system at minimal force will be tested with an SNI model with a control stimulus, a thermal sensitivity ramp, and a 50° C constant temperature. Together, this work validates the ARM system across new pain models, measures the effect of reduced confounds on resulting experimental data, further eliminates potential errors, bias, and experimenter workload through automated aiming, and expands its capacity to include thermal stimuli, allowing for more streamlined somatosensory assay batteries.

Disclosures: J. Burdge: A. Employment/Salary (full or part-time):; Tactorum Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactorum Inc. **I. Abdus-Saboor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactorum Inc. **J.K. Thackray:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tactorum Inc. F. Consulting Fees (e.g., advisory boards); Tactorum Inc.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.20/Z6

Topic: E.01. Somatosensation – Pain and Itch

Support: NIDCR Grant DE022129

Title: Assessment of Spontaneous Pain in Socially Interacting Rodents During the Dark Phase

Authors: *M. UMORIN[1], P. KRAMER[2];
[1]Biomed. Sci., Texas A&M Col. of Dent., Dallas, TX; [2]Biomed. Sci., Texas A&M Univ. Sch. of Dent., Dallas, TX

Abstract: Spontaneous pain measurement is considered the gold standard for assessing pain. In rodents, 70-90% of total activity occurs during the dark phase. However, when housed individually, rodents exhibit elevated stress hormone levels, increased anxiety-like behaviors, and reduced exploratory activity, all of which can confound pain assessments. As a result, current pain measurement approaches may lack accuracy. Although evoked pain testing remains the primary method used in drug development, these limitations may contribute to reduced translational validity. Observing spontaneous behaviors in unrestrained rodents within naturalistic environments that include social interactions over extended periods may help overcome these challenges. To address the limitations of existing methods, we observed freely moving pairs of rats and mice during the dark phase for one hour. Our results demonstrate that multiple anatomical points on two interacting animals can be accurately tracked in complete darkness. This approach enables precise quantification of movement patterns, which may reflect changes associated with spontaneous pain states.

Disclosures: M. Umorin: None. **P. Kramer:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.21/Z7

Topic: E.01. Somatosensation – Pain and Itch

Title: Optical electrophysiology for in vitro investigations of neuronal excitability in chronic pain research

Authors: *P. KARILA, J. SJÖHOLM, A. SKILJE, L. T. AGHOLME, L. MOLL, J. PIHL;
Cellectricon AB, Mölndal, Sweden

Abstract: From a pharmaceutical and translational research standpoint, chronic pain poses unique challenges due to its complex, multifactorial biology and the limited efficacy as well as safety concerns associated with current analgesics. With the increasing need for new drugs for

the treatment of chronic pain, a high-capacity approach to functionally identify and validate novel targets as well as for identifying and progressing new molecules is needed.
As changes in neuronal excitability is a key hallmark of chronic pain, we applied optical electrophysiology, taking advantage of the platform's combination of high-capacity testing with high temporal and optical resolution, to demonstrate that the approach is valuable for in vitro functional validation of pain targets and detailed characterization of drug candidates.
Dorsal root ganglia neurons (DRGs) from adult rats were cultured in a 384-well format and at the day of the experiment, transient calcium elevations were recorded as a response to electric field stimulation on an optical electrophysiology platform. The changes in neuronal excitability were recorded and analysed both on the population level and at the single cell level, which enables an analysis of a drug response from physiologically relevant subpopulations.
Compounds with known mechanisms can be efficiently identified using the high-capacity optical electrophysiology platform and potency determinations performed. IC_{50} determinations for e.g. suzetrigine, ziconotide, and gabapentin fell within the expected range. Further, inflammatory mediators and CIPN-inducing drugs such as oxaliplatin increased the neuronal excitability in the DRG neurons.
To investigate more subtle, modulatory changes in excitability, a single cell analysis was performed. For example, as only a subset of the DRG neurons express TrkA, analysis of the modulation of the NGF-TrkA signalling from a capsaicin-responding subpopulation of neurons reached significance, whereas the change in excitability was not significant in the total cell population.
Using the high-capacity optical electrophysiology approach, we were able to characterize compound effects in an efficient manner, which indicates its utility for validating novel targets and molecules. Further, the ability to apply single cell analysis while maintaining a relatively high capacity also indicates that it is highly suitable for mechanistic studies where subtle, modulatory effects need to be determined. The single cell analysis capability is also cell-sparing, which opens for the functional study of DRGs from different species where the access to cells is more limited, such as humans.

Disclosures: P. Karila: A. Employment/Salary (full or part-time):; Cellectricon AB. **J. Sjöholm:** A. Employment/Salary (full or part-time):; Cellectricon AB. **A. Skilje:** A. Employment/Salary (full or part-time):; Cellectricon AB. **L.T. Agholme:** A. Employment/Salary (full or part-time):; Cellectricon AB. **L. Moll:** A. Employment/Salary (full or part-time):; Cellectricon AB. **J. Pihl:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.22/Z8

Topic: E.01. Somatosensation – Pain and Itch

Title: DRG Transcriptomics across three sciatic nerve injury models uncovers convergent molecular targets

Authors: *E. ESNEAULT[1], F. WITTE[2], Z. MAKOWSKA[2], F. SIMON[2], S. PEDRON[1];
[1]Porsolt, Le Genest St Isle, France; [2]Nuvisan, Berlin, Germany

Abstract: Neuropathic pain remains a major clinical challenge due to its complex pathophysiology and the limited efficacy of current treatments. Preclinical animal models are essential for improving our understanding of the underlying mechanisms and identifying novel therapeutic targets. These models include rat sciatic nerve injury models which are widely used to reproduce key features of peripheral neuropathic pain. The aim of this study was to characterize the expression of a curated panel of 44 molecular targets involved in neuronal excitability, including ion channels, neurotransmitter systems, and sensory receptors implicated in nociceptive signalling, in dorsal root ganglia (DRG) across three widely used rat models of peripheral neuropathic pain. Rats were subjected to Spared Nerve Injury (SNI), Chronic Constriction Injury (CCI), and Spinal Nerve Ligation (SNL). Pain-related behavior was evaluated 14 days after lesion to confirm the development of tactile allodynia and thermal hyperalgesia. Following behavioral testing, ipsilateral DRG were collected and processed for RNA sequencing analysis in comparison to the DRGs from naïve rats. Transcriptomic profiling of the pre-selected target panel revealed a broadly conserved injury-associated expression pattern across all three models compared with naive controls. Of the 44 pre-selected targets 14 genes were significantly differentially expressed in at least one model and 4 genes in all three models ($|FC| \geq 2$, FDR ≤ 0.05). We saw two injury markers (*Atf3* and *Sppr1a)* and the neuropeptide *Npy* with concordant up-regulation across all models and inflammatory mediators (Il6, Ccl2) up-regulated in at least one model. Other neuropeptides (*Tac1*) and ion-channels (*Cacna1h* and *Kcna2*) showed reduced expression compared to the controls. Across the three models, transcript abundance was positively correlated with mechanical hypersensitivity for three canonical myelin sheath genes (*Mbp*, *Mpz*, and *Pmp22*), whereas expression of *Sarm1*, a key mediator of axonal degeneration, showed a negative correlation. These findings show that peripheral nerve injury induces a conserved DRG transcriptional signature characterized by neuroinflammatory activation, neuronal dysfunction, and altered expression of myelin-related genes. Despite differences in the anatomical location and nature of the sciatic nerve lesions, no clear transcriptomic distinctions were observed among the SNI, CCI, and SNL models. These findings highlight the importance of DRG transcriptomic profiling for identifying conserved, model-independent therapeutic targets in neuropathic pain.

Disclosures: E. Esneault: None. **F. Witte:** None. **Z. Makowska:** None. **F. Simon:** None. **S. Pedron:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.23/Z9

Topic: E.01. Somatosensation – Pain and Itch

Title: Culturing Human iPSC-Derived Sensory Neurons with Innervation Targets Remodels the Transcriptional Profile

Authors: *H. MOELLER, P. WALSH, V. TRUONG;
Anatomic Inc., Minneapolis, MN

Abstract: Pain acts through a wide variety of complex mechanisms to alert the body to potential dangers and tissue damage. There are many degrees of pain and variations in the interpretations of painful stimuli, making it a difficult area to study, but still an important one as chronic pain affects about 25% of adults in the United States alone, reducing quality of life and making daily tasks difficult for these individuals. Originating in peripheral tissues, such as skin and muscle, pain is sensed by nociceptive sensory neurons and transmitted to the central nervous system. Human-specific cell cultures with hiPSCs are an effective and scalable tool to study pain circuitry for the discovery of novel therapeutics without the ethical and translational limitations of rodent models. However, hiPSC sensory neurons by themselves are missing specific targets and receptors present in native populations. Co-culture models could meet this limitation by more closely replicating the relevant physiological environments and potentially increasing important targets, thereby providing a platform for analyzing the pain pathway in detail for targeted treatments and drug studies. We cultured hiPSC-derived sensory neurons with multiple tissue types on microfluidic devices to study the effect innervation targets have on gene expression. hiPSC-derived sensory neurons were cultured with three different cell types: primary keratinocytes, primary skeletal muscle, and hiPSC-derived dorsal horn neurons. All cell types were validated by phase contrast morphology, immunocytochemistry (ICC) analysis, and RNA bulk-sequencing. We showed by phase contrast morphology that axons from the sensory neuron chamber extend to their innervation targets within two weeks in culture and further validated the key expression markers for each cell type by ICC. RNA was collected from cells after three weeks of culture and bulk-sequenced, revealing that there are transcriptomic differences in sensory neurons when cultured with other cell types.Here, we demonstrate that the transcriptome of hiPSC-derived sensory neurons can be modulated through co-culture with innervation target cell types, highlighting the importance of cellular context in shaping neuronal identity and function. We established three physiologically relevant co-culture models that will support further research into pain therapeutics.

Disclosures: H. Moeller: A. Employment/Salary (full or part-time):; Anatomic Incorporated. **P. Walsh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **V. Truong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR055.24/Z10

Topic: E.01. Somatosensation – Pain and Itch

Title: Human iPSC-Derived Sensory Neurons with Mature Nociceptive Function for Pain Modeling and Drug Discovery

Authors: G. S. SAHIN[1], J. LAWSON[2], K. JANKE[1], S. MATHIVANAN[4], C. PERRY[3], A. JOHNSON[1], K. XU[5], J. SEO[6], ***L. KONG**[1];
[1]BrainXell, Madison, WI; [2]BrainXell, MADISON, WI; [3]Quality Control, BrainXell, Madison, WI; [4]Ctr. for Neurologic Dis., Sanford Burnham Prebys Med. Discovery Inst., San Diego, CA; [5]BrainXell Inc., Madison, WI; [6]BMS, San Diego, CA

Abstract: Chronic pain is a leading health crisis lacking effective long-term treatments. Animal models suffer from high clinical failure rates due to genomic differences, while human cadaver tissue lacks availability. Human induced pluripotent stem cells (hiPSCs) offer a scalable alternative. In this study, we developed a robust protocol to differentiate hiPSCs into highly pure, functionally mature sensory neurons that demonstrate key features of nociceptors. This method works equally well across male and female hiPSC lines, demonstrating high lot-to-lot consistency and reproducibility across multiple production runs. Immunocytochemistry reveals cultures are >95% positive for Peripherin and β-III Tubulin, >80% for Brn3A, and >90% for NaV1.7 and NaV1.8. To validate nociception-related phenotypes, robust TRPV1 expression was confirmed at transcriptomic and protein levels. TRPV1 functionality was verified via robust calcium influx to the agonist capsaicin, with specificity validated through pharmacological inhibition using Capsazepine. Dose-dependent capsaicin responses were confirmed via microelectrode array (MEA) and whole-cell patch-clamp recordings. Because voltage-gated sodium channels NaV1.7, NaV1.8, and NaV1.9 determine excitability, we tracked their maturation, observing consistently robust mRNA levels. MEA characterization showed these neurons are spontaneously active by day 14, reaching a stable baseline by day 25 with 95% active electrode yield (AEY). Functionally, capsaicin increased mean firing rate and AEY, whereas sensory neuron activity was silenced by selective inhibition of NaV1.7 (Huwentoxin, 30 nM) and NaV1.8 (A803467, 300 nM). These findings demonstrate that our hiPSC-derived sensory neurons provide a reproducible, sex-inclusive, and physiologically relevant model for nociception research. Their scalability, consistent quality, and rapid maturation make them ideal for high-throughput screening platforms to advance novel analgesic discovery.

Disclosures: G.S. Sahin: None. **J. lawson:** None. **K. Janke:** None. **S. Mathivanan:** None. **C. Perry:** None. **A. Johnson:** None. **K. Xu:** None. **J. Seo:** None. **L. Kong:** None.

Poster

PSTR055: Pain Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

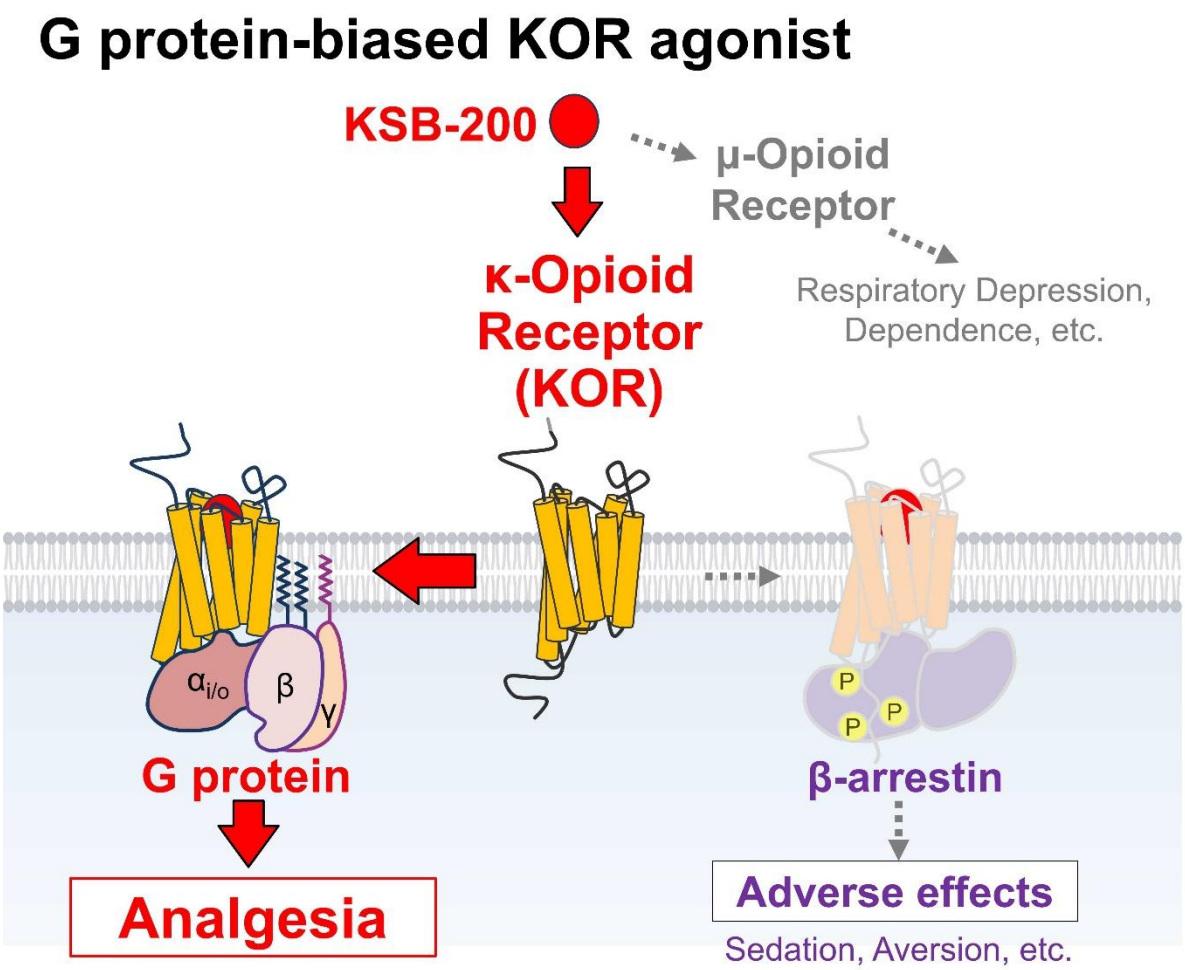
Program #/Poster #: PSTR055.25/Z11

Topic: E.01. Somatosensation – Pain and Itch

Title: A Novel Orally Available G Protein-Biased κ Opioid Receptor Agonist with an Improved Safety Margin for Analgesia

Authors: *K. TAKEO[1], S. FUJII[1], A. IZAWA[1], N. YUZAWA[1], E. HIGASHI[1], H. TSUCHIYAMA[1], Y. OMORI[1], T. NISHI[1], T. HINO[1], T. FUJITA[1], K. KAWAI[1], M. YAMAMOTO[1], T. IWAMURA[2], M. UCHIDA[1];
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Abstract: κ-Opioid receptor (KOR) agonists are considered promising analgesics because they may avoid μ-opioid receptor-mediated adverse effects, such as respiratory depression and drug dependence. However, conventional KOR agonists are known to induce adverse effects in central nervous system, including sedation and aversion, which have been linked to β-arrestin-dependent signaling. Accordingly, G protein-biased KOR agonists are expected to provide effective analgesia with improved tolerability. In this study, we characterized KSB-200, a novel biased KOR agonist, and evaluated its pharmacological and ADMET profile in comparison with the clinically used KOR agonist nalfurafine. G protein signaling was assessed by inhibition of forskolin stimulated cAMP production, whereas β-arrestin 2 recruitment was evaluated using a bioluminescence resonance energy transfer (BRET) assay. KSB-200 behaved as a selective KOR full agonist and exhibited markedly attenuated β-arrestin 2 recruitment, demonstrating a strongly G protein-biased signaling profile even at higher concentration. Oral administration of KSB-200 produced dose dependent analgesic effects in a mouse postoperative pain model. The effective analgesic dose was approximately 100 fold lower than the dose affecting locomotor activity, used as an index of sedation. Furthermore, no evidence of dependence or aversion was observed in the conditioned place preference or conditioned place aversion tests. Pharmacokinetic studies of KSB-200 demonstrated adequate brain penetration and favorable plasma half-life profiles across species. In addition, KSB-200 exhibited acceptable ADME properties and showed no severe findings in standard in vitro and in vivo toxicological assessments. Together, these results indicate that KSB-200 is an orally available, G protein-biased KOR agonist with an improved safety margin between analgesic efficacy and central adverse effects, supporting its potential as a next generation analgesic candidate for the treatment of acute and chronic pain.



Disclosures: K. Takeo: None. **S. Fujii:** None. **A. Izawa:** None. **N. Yuzawa:** None. **E. Higashi:** None. **H. Tsuchiyama:** None. **Y. Omori:** None. **T. Nishi:** None. **T. Hino:** None. **T. Fujita:** None. **K. Kawai:** None. **M. Yamamoto:** None. **T. Iwamura:** None. **M. Uchida:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.01/Z12

Topic: E.01. Somatosensation – Pain and Itch

Support: R01DK142785

Title: Nucleolin promotes neuropathic pain by increasing chromatin accessibility at the Ccl2 promoter in primary sensory neurons

Authors: L. ZHANG[1], R. MA[2], ***Y. TAO**[3];
[1]New Jersey Med. Sch., Newark, NJ; [2]New Jersey Med. School, Rutgers, Bloomfield, NJ;
[3]Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: Nerve injury-induced transcriptional alterations in primary sensory neurons of the dorsal root ganglion (DRG) constitute a key molecular basis for the development of neuropathic pain. Nucleolin (NCL), a highly conserved multifunctional nucleolar protein, regulates gene transcription. Here, we identify that NCL is expressed exclusively in the nuclei of DRG neurons. Peripheral nerve injury time-dependently upregulates *Ncl* mRNA and NCL protein levels in injured DRG neurons. Blocking this upregulation through DRG microinjection of the adeno-associated virus 9 (AAV9) expressing an shRNA targeting *Ncl* attenuates nerve injury-induced increases of C-C motif chemokine ligand 2 (CCL2) mRNA and its protein in injured DRG and alleviates the development and maintenance of mechanical, heat and cold hypersensitivities. Conversely, mimicking DRG NCL upregulation through DRG microinjection of AAV9 carrying the full-length *Ncl* coding sequence increases *Ccl2* mRNA and CCL2 protein levels in microinjected DRGs and produces neuropathic pain-like symptoms in the absence of nerve injury. Mechanistically, peripheral nerve injury increases NCL occupancy at the *Ccl2* promoter and enhances chromatin accessibility at this locus, resulting in elevated CCL2 expression in DRG neurons, which is reversed by NCL knockdown. Given that *Ncl* mRNA is co-expressed with *Ccl2* mRNA in individual DRG neurons, our findings suggest that NCL upregulation in the DRG contributes to neuropathic pain likely by increasing chromatin accessibility at the *Ccl2* promoter in primary sensory neurons.

Disclosures: L. Zhang: None. **R. Ma:** None. **Y. Tao:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.02/Z13

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH-5R01NS128410

Title: CaMKII Activity Regulates Excitability of Dorsal Root Ganglion Neurons and Controls Neuropathic Pain

Authors: *Y. LIU, S. WU, T. CHENG, D. MUELLER, B. PAN;
Dept. of Neurobio., Univ. of Texas Med. Br., Galveston, TX

Abstract: Objective
Peripheral nerve injury produces persistent neuropathic pain associated with hyperexcitability of

dorsal root ganglion (DRG) sensory neurons. Previous work from our laboratory showed that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) activity is markedly reduced in DRG neurons after nerve injury. Here we tested the hypothesis that **CaMKII activity directly regulates the intrinsic excitability of DRG neurons and thereby controls neuropathic pain. Methods**
Neuropathic pain was induced in rats using tibial nerve injury (TNI). CaMKII signaling in L4-L5 DRG neurons was manipulated using adeno-associated viral (AAV) vectors. To inhibit CaMKII, we expressed the CaMKII autocamtide-2-Related Inhibitory Peptide (AIP, AAV-AIP). To increase CaMKII activity, we expressed a constitutively active mutant CaMKII with threonine 286 mutated to aspartate (AAV-CaMKII-T286D). Pain-related behaviors were evaluated using von Frey, pin-prick, acetone, and brush tests. Intrinsic neuronal excitability was assessed using whole-cell patch-clamp recordings in acutely dissociated DRG neurons. **Results**
TNI produced robust mechanical and cold hypersensitivity and increased excitability of ipsilateral DRG neurons, characterized by decreased rheobase and increased input resistance. Viral inhibition of CaMKII activity with **AAV-AIP in naïve rats increased DRG neuron excitability and induced pain-like behaviors**, mimicking the neuropathic phenotype. In contrast, restoring CaMKII signaling with **AAV-CaMKII-T286D in DRG neurons reduced neuronal hyperexcitability and reversed behavioral hypersensitivity after TNI. Conclusion**
These findings demonstrate that **CaMKII activity is a key regulator of the intrinsic excitability of DRG sensory neurons.** Loss of CaMKII activity promotes neuronal hyperexcitability and pain, whereas restoring CaMKII activity normalizes excitability and alleviates neuropathic pain. Targeting CaMKII signaling in peripheral sensory neurons may therefore represent a promising strategy for treating chronic neuropathic pain.

Disclosures: Y. Liu: None. **S. Wu:** None. **T. Cheng:** None. **D. Mueller:** None. **B. Pan:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.03/Z14

Topic: E.01. Somatosensation – Pain and Itch

Support: SECIHTI grant CBF-2025-I-1460

Title: TLR4 activation induces mechanical allodynia in REM sleep-deprived rats via augmenting TRPV1 expression and functioning in dorsal root ganglion neurons

Authors: *C. MARTÍNEZ MAGAÑA[1,2], V. M. GALINDO AVENDAÑO[3], A. ALMANZA[4], J. MURBARTIÁN[5];
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Abstract: TLR4 has been linked to several chronic inflammatory diseases and pathological pain. In addition, TLR4 activation promotes TRPV1 channel activity, an important transducer of thermal and chemical noxious stimuli in nociceptors. We previously reported that rapid eye movement sleep deprivation (REMSD) leads to mechanical allodynia, which is promoted by NF-κB activity. This study aimed to determine whether TLR4, a well-recognized upstream activator of NF-κB, contributes to the development of REMSD-induced mechanical allodynia in rats, likely by enhancing TRPV1 expression and function. Data showed that REMSD increased TRPV1 protein expression in the spinal cord and dorsal root ganglion (DRG) neurons. Moreover, LPS-RS, a TLR4 antagonist, and A784168, a TRPV1 blocker, reduced established REMSD-induced allodynia. Pretreatment with LPS-RS (prior to the rats being subjected to REMSD) reduced the development of mechanical allodynia in rats and, interestingly, reduced the antiallodynic effect of A784168 and diminished the REMSD-induced upregulation of TRPV1. To determine whether TLR4 activation enhances TRPV1 function in REMSD rats, we isolated DRG neurons from naïve and REMSD rats. Data obtained show that DRG neurons from REMSD rats exhibit enhanced capsaicin-induced calcium currents compared with those from naïve rats, supporting the notion that REMSD increases TRPV1 function. Interestingly, in DRG neurons from LPS-RS-pretreated rats, capsaicin-induced calcium currents were similar to those in rats without REMSD. Our data support the idea that TLR4 activation plays an important role in the development of mechanical allodynia induced by REM sleep deprivation in rats, enhancing TRPV1 expression and functionality.

Disclosures: C. Martínez Magaña: None. **V.M. Galindo Avendaño:** None. **A. Almanza:** None. **J. Murbartián:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.04/Z15

Topic: E.01. Somatosensation – Pain and Itch

Support: VA-MD College of Veterinary Medicine Internal Research Competition

Title: The effects of nicotine treatment and neuropathic injury on the subcellular and surface behavior of theα6 nicotinic receptor subunit in the mouse dorsal root ganglia.

Authors: *A. MANN[1], J. S.[1], R. L. PARKER[2];
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Abstract: In 2023, 24% of US adults experienced chronic pain, yet current treatments are ineffective. Nicotine (nic), a nicotinic acetylcholine receptor (nAChR) agonist, provides

analgesia short-term, but chronic use exacerbates pain. While it is known that nAChRs are downregulated during pain states in the dorsal root ganglia (DRG), the mechanisms are not well described. Understanding how both pain and nic treatment alter α6 nAChR behavior can provide insight into whether nAChR upregulation is a viable target for chronic pain. All experiments used transgenic mice of both sexes with GFP-labelled α6 nAChRs (α6-GFP). Sex differences were not examined. We examined α6 nAChR subcellular localization in DRG neurons using the α6-GFP subunits following Spared Nerve Injury (SNI) using immunohistochemistry and confocal microscopy, $n = 9$ mice, controls $n = 4$. We calculated colocalization by subtracting endogenous α6-GFP signal from the organelle markers (tM_2) in FIJI, with a lower number signifying more overlap. Next, we examined α6-GFP fluorescence in cultured primary adult neurons incubated in media, 50 nM nic, 500 nM nic, or 50 mM mecamylamine (mec), a nonspecific nAChR antagonist, and imaged via confocal microscopy. The corrected total cell fluorescence by area (CTCF) was calculated by subtracting background fluorescence from total cell fluorescence and divided by cell size to quantify α6 nAChR presence, $n = 513$ cells. Lastly, we examined α6 nAChRs on or near the cell membrane for 1 minute with HILO imaging following 24-hour incubation of primary adult neurons in media, 50 nM nic, or 500 nM nic. Deconvolution and binary tracking were performed for localization, $n = 1015$ particles. In SNI treated mice, Golgi, endosomes, endoplasmic reticulum, and GFP autofluorescence were examined, $tM_2 = 0.14$, 0.22, 0.18, and 0.22, respectively. Controls were similar at $tM_2 = 0.13$, 0.23, 0.21, and 0.24. Following nic and mec treatment, CTCF = 201.9 ± 6.8, 121.9 ± 12, 90.1 ± 10.0, 49.2 ± 5.5 for untreated, 50 nM, 500 nM, and 50 mM mec respectively. A one-way ANOVA found a significant difference between groups ($p<0.0001$). In the HILO imaging experiment, neurons in 50 nM nic showed increased receptor velocity compared to both 500 nM nic treated and untreated cells, yet total path length did not change. While α6 subcellular localization did not change following SNI treatment, there were clear differences following nic and mec administration in total expression and membrane behavior. Therefore, nic may have different effects on DRG α6 nAChRs compared to midbrain dopaminergic neurons. Future studies will examine interactions between nic administration and chronic pain to better understand the role of α6 in pain.

Disclosures: A. Mann: None. **J. S.:** None. **R.L. Parker:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.05/Z16

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 2R01NS114018-07

Title: Mitochondrial reprograming of translation during painful diabetic neuropathy

Authors: *A. R. MEYER, G. GARCÍA, A. MIKESELL, Z. CAMPBELL;
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Abstract: Pain is a hallmark of diabetic neuropathy. We previously published that the reactive metabolite methylglyoxal (MGO) sensitizes dorsal root ganglia neurons via the stress-sensitive kinase GCN2 (Meyer et al., 2025). GCN2 activates a conserved translational control mechanism termed the integrated stress response (ISR). Here, we asked how GCN2 is activated and identified downstream targets using functional genomics. MGO disrupts complex I of the electron transport chain through generation of advanced glycation end products. Disruption of complex I results in an imbalance in the NADH/NAD+ ratio. Restoring NAD+ levels prevents activation of the ISR. GCN2 is required for mechanical sensitization both by MGO and following ablation of beta cells by streptozotocin in mice. The data suggest that metabolic dysfunction can trigger GCN2-dependent alterations in protein synthesis in humans and in rodents that drive a nociceptive pattern of translational control.

Disclosures: A.R. Meyer: None. **G. García:** None. **A. Mikesell:** None. **Z. Campbell:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.06/Z17

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH grant R01NS128403-04

Title: Orai3 regulates calcium signaling and pain hypersensitivity in sensory neurons

Authors: *X. LI[1,2], F. HARERAM[3], Y. MEI[2], Y. TAO[2], H. HU[2];
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Abstract: Orai3 regulates calcium signaling and pain hypersensitivity in sensory neurons Xiang Li, Qiao Zhang, Jingsheng Xia, Yixiao Mei, Xinghua Gao, Yuan-Xiang Tao, Huijuan Hu.Department of Anesthesiology, Rutgers University, Newark, New Jersey 07103 Chronic pain affects approximately 10% of the global population and remains difficult to treat because of the limited efficacy and adverse effects of current therapies. Neuropathic pain arises from maladaptive peripheral and central sensitization. Ca^{2+}-permeable channels in neurons and glial cells are critical for the induction and maintenance of pain hypersensitivity. Ca^{2+} release-activated Ca^{2+} (CRAC) channels consist of three pore-forming subunits, Orai1/2/3. Among them, Orai3 is unique in mediating store-independent calcium entry in non-excitable cells and has been implicated in multiple diseases. However, compared with Orai1, the pathological role of Orai3 remains poorly understood. Our previous studies showed that Orai3 is expressed in the spinal cord and dorsal root ganglion (DRG) neurons and is upregulated under several chronic pain conditions, including collagen-induced arthritis, complete Freund's adjuvant-induced

inflammatory pain, and spared nerve injury (SNI). However, whether Orai3 contributes to chronic pain development remains unknown.In this study, we investigated the role of Orai3 in neuropathic pain using global Orai3 knockout (KO) mice. In the SNI model, Orai3 KO mice exhibited reduced mechanical allodynia and thermal and cold hypersensitivity beginning on post-injury day 3 compared with wild-type (WT) SNI mice. In a high-fat diet (HFD)/streptozotocin (STZ)-induced type 2 diabetes model, Orai3 deficiency attenuated mechanical allodynia and thermal and cold hypersensitivity. These behavioral changes were accompanied by increased Orai3 and STIM1 expression in the spinal cord and DRG, as well as increased phosphorylation of ERK1/2 and JNK in the spinal cord. These molecular alterations were markedly attenuated in Orai3 KO mice subjected to the same HFD/STZ model. Together, our findings reveal a previously unrecognized role of Orai3 in neuropathic pain and suggest that Orai3 contributes to painful diabetic neuropathy and spinal sensitization.
Keywords: Chronic pain, neuropathic pain, Orai3, spinal cord, DRG, neuron.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.07/Z18

Topic: E.01. Somatosensation – Pain and Itch

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Title: Temporal Gene Expression Patterns and Enriched Biological Pathways in a Rat Model of Full-Thickness Thermal Injury

Authors: K. PAGTAMA[1], M. G. DUNKELBERG[2], T. OLAOLUWA[3], G. SERRANO-BERRIOS[2], M. J. IADAROLA[2], D. L. AVERITT[4], A. J. MANNES[2], M. R. SAPIO[2], ***T. GOTO**[1];
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Abstract: Thermal burn injury is a form of tissue damage caused by exposure to excessive heat. Pain is a major clinical problem in patients with burn injury because it restricts mobility and functional recovery, delays wound healing, and impairs quality of life. To better understand the mechanisms underlying burn pain, it is essential to characterize the biological trajectory of pain associated with injury-induced immune responses and transcriptomic changes related to

signaling among damaged tissue, sensory neurons, and immune cells. We aimed to identify gene clusters with distinct temporal expression patterns and characterize their associated biological pathways to better understand burn pain at the biological and molecular levels. A 100°C soldering iron tip was applied to the plantar surface of the right hind paw for 30 seconds to generate a full-thickness thermal injury and induce hyperalgesia. Thermal hyperalgesia was assessed. The hind paw tissues collected at 6 hours, 72 hours, and 1 week post-injury were subjected to RNA sequencing (RNA-seq) analysis. Burn-side RNA-seq data were analyzed with DESeq2. Time-dependent genes were identified by likelihood-ratio testing and filtered for an absolute log2 fold change ≥ 1 in at least one comparison versus baseline. Variance-stabilizing transformation-normalized expression was averaged by time point, converted to gene-wise z-scores, and clustered by k-means (k = 7). KEGG over-representation analysis was then performed for each cluster using clusterProfiler. Thermal hyperalgesia progressively worsened over time (6 h, 72 h, and 1 week), with the greatest increase in response time from baseline observed at 1 week, indicating maximal pain sensitivity at this time point. Among the seven gene clusters identified, two showed progressively increasing expression that peaked at 1 week. Over-represented KEGG pathways in these clusters included cytokine-cytokine receptor interaction and neuroactive ligand-receptor interaction. Our data suggest that thermal hyperalgesia following burn injury is associated with distinct temporal changes in gene expression, particularly in pathways related to immune and inflammatory signaling and neuronal communication. An integrated gene expression and pain sensitivity provides new insight into the biological and molecular mechanisms regulating burn-related pain behaviors and may help identify potential therapeutic targets for pain management.

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Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.08/Z19

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS130608

Title: Investigating endogenous GABA synthesis in the human dorsal root ganglion

Authors: *J. A. O'BRIEN[1], C. E. MOORE[1], F. BIAN[2,3], T. J. PRICE[1];
[1]Dept. of Neurosci. and Ctr. for Advanced Pain Studies, [2]Dept. of Bioengineering, Erik Jonsson Sch. of Engin. and Computer Sci., [3]Office of Res. and Innovation, Univ. of Texas at Dallas, Richardson, TX

Abstract: GABA receptors are expressed in the dorsal root ganglion, and their modulation has been shown to have functional effects on nociceptive signaling. In rodents, this has been linked to the expression of canonical enzymes such as GAD65 and GAD67. However, the direct presence of GABA has not yet been conclusively demonstrated in the human dorsal root ganglion (hDRG), nor has the presence of canonical GABA biosynthetic machinery. Firstly, we aimed to investigate the presence of endogenous GABA within the hDRG. We used fresh-frozen lumbar hDRG samples (n = 2; one 48-year-old male and one 20-year-old female) from organ donors without a history of neuropathy or neurological disease, which were frozen within four hours post-mortem. We utilized desorption electrospray ionization mass spectrometry imaging combined with *in situ* Katritzky reaction-based derivatization of primary amines to generate spatial images of GABA in tissue sections. Sham derivatization protocols were used as negative controls; human spinal cord and spotted volumes with known concentrations of GABA were used as positive controls. We found that GABA is detectable in hDRG samples at expression levels lower than that of the spinal cord dorsal horn. By overlaying mass spectrometry images and hematoxylin and eosin histological staining, we determined that GABA expression was highest in neuronal soma-rich hDRG regions and appeared to overlap with the satellite envelope. Next, to investigate the potential biosynthetic pathways responsible for endogenous GABA production and release, we analyzed previously published hDRG single-cell and single-nuclei RNA sequencing data sets to determine the expression levels of enzymes belonging to these pathways. We found that the genes encoding the canonical enzymes *GAD1* (GAD67), *GAD2* (GAD65), and *SLC32A1* (VGAT) were lowly expressed or absent in all neuronal and non-neuronal cell types. However, genes involved in the arginine-ornithine-putrescine pathway for GABA biosynthesis, such as *MAOA*, *MAOB, DAO*, *ODC1,* and *ALDH1A1*, were expressed in multiple neuronal and non-neuronal cell subpopulations. These results provide support for local GABAergic signaling in the hDRG that may modulate somatosensory signals before reaching the central nervous system. This provides justification for investigating the therapeutic modulation of DRG GABAergic signaling in the context of pain by using peripherally restricted drugs targeting non-canonical GABA biosynthetic pathways.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.09/Z20

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant U19NS130608

Title: Chromatin landscape remodeling in painful diabetic neuropathy in human dorsal root ganglia and spinal cord

Authors: *Ú. FRANCO-ENZÁSTIGA[1], K. MAZHAR[1], S. TOIKUMO[2], L. HE[1], R. RAVIRALA[1], K. DOMALOGDOG[1], H. MYDUGOLAM[1], S.-R. ODOI[1], O. DIBOU[1], A. RAVIRALA[1], T. J. PRICE[1];
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Abstract: Diabetic peripheral neuropathy (DPN) is one of the most preponderant and severe complications of diabetes mellitus, and the most frequent form of damage to the peripheral nervous system. Around 30-50% of patients with diabetic neuropathy develop neuropathic pain. Here, we explore how the epigenome is remodeled in individuals with painful DPN compared with controls by profiling the chromatin landscape of human dorsal root ganglia (hDRG) and spinal cord (hSC) using spatial ATAC-seq. Pseudo-bulk differential analysis showed pervasive chromatin changes in hDRG. Among the top genes with increased chromatin accessibility in DPN, we identified neurexin and Major Histocompatibility Complex (MHC) class II genes. Transcription factor binding site (TFBS) analysis showed enhanced sites for AP-1 transcription factors and ATF4. In neurons, pathway and gene ontology analyses revealed increased accessibility for type I IFN receptor and $GABA_A$ receptor genes. Chromatin remodeling in hSC also showed remodeling in DPN with neurons and microglia contributing to a substantial proportion of the effect. Similar to hDRG, AP-1 binding sites were found increased in hSC in neurons, while CTCF TFBSs were reduced, potentially contributing to chromatin architecture disruption. Leveraging both chromatin accessibility datasets, we next examined ligand-receptor pairs involving ligands upregulated in hDRG in DPN and receptors with accessible chromatin in hSC. We found that Fibroblast Growth Factor (FGF) genes, neurexin and interferon alpha genes play important roles in cell-cell communication networks in painful DPN. Finally, we also tested for enrichment of chronic pain GWAS loci in differentially accessible genes. Among the top genes associated with chronic pain risk showing increased chromatin accessibility in hDRG in DPN were *DCC* and *NRXN1*. Our findings demonstrate that DPN is associated with alterations in the chromatin landscape of the hDRG and hSC, which may underly DPN pathophysiology.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant 5R01NS102161-05

Title: Prolactin receptor long isoform expression is reduced in the dorsal root ganglia of humans with chronic pain

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Abstract: Chronic pain is a medical problem that is overrepresented in women. Previous rodent and human studies found that prolactin contributed to sensory neuron excitability in dorsal root ganglion (DRG), thus leading to nociceptive transmission. More recent studies have focused on the differential roles of the short and long isoform of prolactin receptors (PRLR) in chronic pain in rodents. Specifically, prolactin receptor short form (PRLR-S) activity is upregulated in the DRG neurons, while prolactin long form (PRLR-L) activity is dampened or unchanged. In this study, we aimed to understand the contribution of PRLR isoforms in human pain by characterizing the isoforms in DRG tissues recovered from organ donors. We used three healthy human donors from each sex and three female donors with a history of chronic pain and performed RNAscope *in situ* hybridization (ISH) to characterize the expression of *PRLR-S* and *PRLR-L* in *TRPV1*-positive sensory neurons. Probes were used against *PRLR-L* (long variant, ΔS1), *PRLR-S* (S1a, S1b, Δ7/11), and *TRPV1*. Human cervical tissue was used as a positive control to validate the PRLR ISH probes. Our results demonstrate human DRG neurons express more PRLR-L than PRLR-S in both sexes, with female donors expressing more PRLR overall. Females with a history of chronic pain expressed significantly less PRLR-L than healthy females. This result is consistent with previous studies in pain models in female mice. Our findings provide evidence that PRLR-L form is the major isoform expressed in human DRG neurons, that this expression is higher in females than in males, and that PRLR-L expression is suppressed in chronic pain conditions in females.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.11/Z22

Topic: E.01. Somatosensation – Pain and Itch

Title: Microglia-Like Cells in Human Dorsal Root Ganglia

Authors: *K. MAZHAR[1], T. J. PRICE[2];
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Abstract: Introduction. Microglia-like macrophages in the satellite envelope of peripheral ganglia have been recorded previously, and recent findings have described a satellite macrophage population in dorsal root ganglia sharing transcriptomic features with microglia. The function of these cells, and the mechanisms by which they may influence neurons in neuropathy are still unclear. Methods. Transcriptomic datasets with single-cell resolution (86 samples from 92 donors) and spatial data (16 samples from 6 donors) were analyzed to characterize gene expression patterns and localization of cell types in human dorsal root ganglia, along with changes with diabetic neuropathy. Results. We observed that the dominant population of macrophages in dorsal root ganglia expressed classical microglia makers such as TMEM119 and P2RY12, as previously described. These microglia-like cells localized to the perineuronal space like satellite glia. They are transcriptomically distinct from all glial cell types and cluster with classical macrophages. They also exhibit significant changes in gene expression, localization, and predicted signaling with diabetic neuropathy. Conclusions We characterize microglia-like cells in human dorsal root ganglia and predict their functions along with changes in diabetic neuropathy. These cells likely play a critical role in pathologic changes that happen in the ganglia with neuropathy.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.12/Z23

Topic: E.01. Somatosensation – Pain and Itch

Support: R01NS131571

Title: Regulation of mTORC1 and mTORC2 signaling by mitochondrial uncoupling coordinates stress-induced translation and cytoskeletal remodeling in immortalized human sensory neurons

Authors: *J. J. AMES[1], E. C. ADDLESON[1], D. C. MOLLIVER[2];
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Abstract: Metabolic remodeling of sensory neurons is increasingly implicated in the transition from acute to chronic pain, yet mechanisms linking mitochondrial dysfunction to nociceptor plasticity remain unclear. Hyperactivation of baseline mTORC1 translation machinery drives local protein synthesis in nociceptors, typically associated with hyperalgesic priming and chronic hypersensitivity, whereas global inhibition reduces pain. AMPK is antihyperalgesic and classically antagonizes mTORC1. We previously demonstrated that the mitochondrial uncoupler BAM15 suppresses nociceptor excitability in vitro and alleviates hyperalgesia *in vivo*, while enhancing mitochondrial respiration and glycolysis by dephosphorylating pyruvate dehydrogenase (PDHA1) and activating AMP-activated protein kinase (AMPK). Here, we expanded a quantitative phospho-proteomic analysis in human DRG-derived HD10.6 cells to

interrogate how BAM15 reshapes translation and cytoskeletal remodeling. Pathway analysis (KEGG, StringDB) revealed parallel co-regulation of both signaling axes driven by a significant (log2FC 2.5 $p<0.0001$) increase in phosphorylation of an activating AMPK substrate site on mTOR (S1261). BAM15 drove phosphorylation of the p90 ribosomal S6 kinase RSK1 (S380), and TSC2 (S1338, S1002, S923) and RPTOR (S722), suggesting removal of mTORC1 inhibition. Coordinated regulation of mTORC1 and translation machinery (eIF4G3, eIF4ENIF1, eIF4B) may indicate a selective stress-induced translational program. In parallel, BAM15 promoted regulation of mTORC2, evidenced by phosphorylation of RICTOR (S1385). Downstream of mTORC2, we identified Rho GTPase-driven actin remodeling by substantial phosphorylation shifts in Rho regulators, including the regulation of Rho GTPase-activating proteins ARHGAP35 (S770) and ARHGAP17 (S161), alongside the exchange factors ARHGEF40 (S371) and ARHGEF17 (S914). We observed dephosphorylation of the nucleoside diphosphate kinase NME1 (S120/122), which produces GTP for activation of G proteins. Regulation of microtubule remodeling was indicated by phosphorylation of Microtubule-Associated Protein 2 (MAP2; T1254). These data suggest that mitochondrial uncoupling coordinates parallel mTORC1/mTORC2 stress responses. Ongoing studies are examining how metabolic stress-induced translational and cytoskeletal reorganization contributes to antinociceptive actions of BAM15.

Disclosures: J.J. Ames: None. **E.C. Addleson:** None. **D.C. Molliver:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

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Topic: E.01. Somatosensation – Pain and Itch

Support: R01NS109936
R01NS131571

Title: Phosphoproteomic analysis of Epac signaling in immortalized human sensory neurons

Authors: *M. TOMASCH[1], J. J. AMES[2], E. ADDLESON[1], D. C. MOLLIVER[3];
[2]Ctr. for Cell Signaling, [3]Dept. of Biomed. Sci., [1]Univ. of New England, Biddeford, ME

Abstract: Hyperalgesic priming is a model of the transition to chronic pain in which an initial injury resolves but leaves subjects vulnerable to an exaggerated response to subsequent injury. In this model, the secondary insult typically involves activation of Gs-coupled receptors with enhanced activation of cAMP effector Epac1/2. Our findings have also implicated Epac2 in acute nociceptor sensitization. Epacs are guanine nucleotide exchange factors that canonically activate the small G protein Rap1 and Rap-dependent protein kinase C (PKC) signaling in sensory neurons, but the downstream effectors and targets of Epac signaling are not well characterized. To identify novel targets of Epac signaling with potential relevance to human pain conditions,

we performed quantitative phospho-protein mass spectrometry in the human dorsal root ganglion-derived HD10.6 cell line, which possesses many molecular features of nociceptors. HD10.6 cells differentiated for 7 days were treated with Epac1/2 activator 8Cpt-AM (n=4) or vehicle (n=3). Phospho-peptides were enriched through 2-stage affinity chromatography prior to analysis by TMT-labeled mass spectrometry. 7807 unique phosphosites were identified, 157 significantly upregulated and 92 downregulated (log2 fold change >1; $p<0.05$). Gene ontology analysis revealed strong enrichment in categories related to cytoskeletal remodeling and small G-protein signaling. The most highly regulated target was SEC22B (32-fold upregulation of pS137), a protein involved in vesicle trafficking and membrane fusion. SEC22B was previously reported to be strongly phosphorylated in response to liver glucagon signaling, suggesting this may be a fundamental target of Gs-coupled receptor signaling. Epac activation also induced a 7-fold downregulation of MAP3K7 (TAK1) phosphorylation at S455, suggesting that TAK1 is strongly regulated by Epac signaling. TAK1 inhibition has been reported to reverse mechanical and thermal hypersensitivity in three preclinical pain models (inflammatory, neuropathic, and primary pain) and prevent hyperalgesic priming. To identify kinases contributing to the profile of Epac activation, Rokai Explorer (v.1.0.0) was used for Kinase-Substrate Enrichment Analysis. Surprisingly, top predicted upregulated kinases included protein kinase G and Aurora kinases; the most strongly downregulated kinase was AMP kinase, a key regulator of metabolic processes reported to be anti-hyperalgesic in priming models. These findings identify novel targets of Epac signaling that may contribute to acute nociceptor sensitization and/or the establishment of chronic pain states.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.14/AA1

Topic: E.01. Somatosensation – Pain and Itch

Title: Multi-view interpretable machine learning reveals a 22-gene transcriptomic signature and hierarchical regulatory network of pain states in the human dorsal root ganglion

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Abstract: Chronic pain affects 20-30% of the global population, yet diagnosis remains reliant on subjective assessments without objective molecular biomarkers. Single-nucleus RNA sequencing (snRNA-seq) enables high-resolution characterization of dorsal root ganglion (DRG) cellular heterogeneity and pain-associated transcriptional reprogramming, but translating sparse, high-dimensional data into robust and interpretable clinical models remains challenging. Here, we developed a multi-level interpretable ensemble learning framework integrating cell type-aware

multi-view pseudobulk feature engineering, bidirectional gene and view selection, bootstrap-based stability analysis, and training-set threshold calibration. Using 85 rigorously quality-controlled human DRG snRNA-seq samples, we identified a 22-gene pain classification panel. The model achieved strong performance (LOOCV AUC 0.8665; holdout AUC 0.8794), with improved class balance through adaptive threshold calibration. SHAP analysis identified HOPX, AGT, and CCDC92 as key drivers: HOPX reflects transcriptional reprogramming and cell state transitions linked to neuroinflammation and glial activation; AGT represents local renin-angiotensin signaling that modulates nociceptor sensitization and inflammatory responses; and CCDC92 implicates cytoskeletal organization and metabolic-stress coupling in neuronal resilience. Gene synergy analysis demonstrated non-redundant, complementary effects across the panel. Co-expression network analysis revealed coordinated interactions among these genes, suggesting a hierarchical regulatory architecture underlying DRG pain states. Together, this work defines a robust molecular signature for chronic pain and establishes a generalizable framework—stability selection, threshold calibration, and network interpretation—for small-sample, high-dimensional biomedical data.

Disclosures: A. Wangzhou: None. **T.J. Price:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.15/AA2

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH HEAL grant NIDCR R01 DE033647

Title: Schwann Cell PPARγ Governs Peripheral Nerve Integrity and Sensory Homeostasis in Health and Cisplatin-Induced Neuropathy

Authors: *V. UZONWANNE[1,2], X. SHI[1,2], N. LIU[1,2], Z. GONG[1,2], Y. YE[1,2,3];
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Abstract: Schwann cells (SC) are essential for nerve function, myelination, and repair, yet their intrinsic signaling pathways remain underexplored. Peroxisome proliferator-activated receptor gamma (PPARγ) regulates lipid/glucose metabolism, but the role of SC PPARγ signaling in pain processing has not been established. Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting effect of platinum-based therapies, including cisplatin (Cis), with pathogenesis linked to mitochondrial stress, myelin disruption, oxidative damage, and dysregulated neuron-glial signaling. We hypothesized that SC PPARγ is necessary for nerve integrity and that its loss may lead to mitochondrial dysfunction, lipid dysregulation, and neuropathic pain contributing to CIPN. *Pparg* SC conditional knockout (cKO) mice (Mpz-Cre; *Pparg*$^{fl/fl}$) and Cre-negative

littermate control mice (*Pparg*$^{fl/fl}$) underwent von Frey mechanical allodynia and thermal latency testing. Sciatic nerve ultrastructure was examined by TEM, and RNA-seq was performed on dorsal root ganglia (DRG) and SC isolated from cKO and control mice. Human SC were exposed to Cis (10 μM, 6 h), and *PPARG, PGC1A,* and *SOD2* expression was assessed by qPCR. Cell viability was measured by MTS assay. Seahorse XF, MitoSOX, BODIPY 493/503, and C11-BODIPY measured bioenergetics, mitochondrial ROS, lipid droplets, and lipid peroxidation, respectively. Elb00824 (Elb; 10 μM), a PPARγ agonist, was examined with Cis in vitro. In tumor-bearing mice with Cis-induced neuropathy, Elb (10 mg/kg, i.p.) was injected daily, and allodynia was evaluated by von Frey one-hour post-treatment.
Pparg cKO mice exhibited heightened mechanical and thermal sensitivity. TEM revealed abnormalities in myelinated fibers and Remak bundles, showing SC PPARγ is required for peripheral nerve integrity under physiological conditions. RNA-seq identified signatures consistent with sensory signaling, glial reactivity, and SC stress. Cis disrupted the PPARγ-mitochondrial axis in SC, reducing *PPARG* and *PGC1A* and upregulating *SOD2*. Cis impaired respiratory capacity, elevated mitochondrial ROS, and induced lipid accumulation and peroxidation. Elb restored *PPARG* and *PGC1A* expression, improved maximal respiration, and reduced mitochondrial ROS, lipid accumulation, and peroxidation. In tumor-bearing mice, Elb attenuated Cis-induced hypersensitivity without affecting tumor growth. Together, these findings establish SC PPARγ as a regulator of mitochondrial-lipid homeostasis, nerve integrity, and sensory function in health and CIPN and identify PPARγ activation as a candidate therapeutic strategy for CIPN.

Disclosures: V. Uzonwanne: None. **X. Shi:** None. **N. Liu:** None. **Z. Gong:** None. **Y. Ye:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.16/AA3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R21NS125484
NIH Grant P20GM152330

Title: In Vitro Chemogenetic Stimulation of Satellite Glial Cells with C21 Drives Glial Activation

Authors: *L. PREECE[1], A. FRENCH[1], L. F. QUEME COBAR[2];
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Abstract: Numerous studies report an association between exposure to chronic stress and an increased risk of developing chronic pain. However, the mechanisms by which stress drives the transition from acute to chronic pain remain poorly understood. At the cellular level, Satellite Glial Cells (SGCs) are essential support cells that envelop sensory neurons in the dorsal root

ganglia (DRGs) and play a critical role in pain processing. In several rodent models of pain, including inflammatory and neuropathic pain, increased sensory neuron excitability has been linked to increased SGC activity. SGC activation is a poorly characterized phenomenon marked by increased expression of glial fibrillary acidic protein (GFAP). Recently, our laboratory developed a chronic stress model in mice based on Loss of Environmental Enrichment (LoEE), which recapitulates a chronic stress phenotype. LoEE alone induces mechanical hypersensitivity. Moreover, mice exposed to LoEE exhibit prolonged pain-related behaviors following a hindlimb ischemia-reperfusion injury. This correlates with increased GFAP expression in SGCs in DRG sections from mice exposed to LoEE. RNA sequencing of SGCs isolated from LoEE-exposed mice revealed significant upregulation of several genes, including GFAP and others associated with pro-inflammatory processes. To better understand the role of SGC activation, our laboratory used a mouse line expressing hDM3q (Gq) Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) under control of a tamoxifen-inducible Cre recombinase (FABP7-Cre-ER). SGCs isolated from these animals were treated with a DREADD agonist (C21) in vitro and showed calcium transients within 2 minutes of exposure to 0.2 µg/µL of C21. After 24h of exposure to a DREADD agonist, these cells also showed increased GFAP expression. These findings suggest that chemogenetic stimulation of DREADD-expressing SGCs is sufficient to induce SGC activation, providing a powerful tool and a potential model to investigate the role of SGC activation in the development of chronic pain. This work was supported by NIH grants R21NS125484 and P20GM152330.

Disclosures: L. Preece: None. **A. French:** None. **L.F. Queme Cobar:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR056.17/AA4

Topic: E.01. Somatosensation – Pain and Itch

Support: R01 DK142785/DK/NIDDK NIH HHS/United States
R01 NS111553/NS/NINDS NIH HHS/United States
R01 NS117484/NS/NINDS NIH HHS/United States

Title: RNA-binding protein MBNL2 mitigates neuropathic pain after chemotherapy through destabilizing CCR2 expression in primary sensory neurons

Authors: *R. MA[1], Y. TAO[2];
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Abstract: Chemotherapy drug-induced changes of gene expression in the dorsal root ganglion (DRG) are critical for the genesis of chemotherapy-induced neuropathic pain (CINP). However, the mechanisms driving these changes remain elusive. Here, we report the downregulation of

muscleblind-like protein 2 (MBNL2), an RNA-binding protein, in the DRG neurons after intraperitoneal injection of paclitaxel. Rescuing this downregulation blocks an increase of the C-C chemokine receptor type 2 (CCR2) in the DRG and mitigates paclitaxel-induced mechanical allodynia, heat and cold hyperalgesia and ongoing pain. Conversely, DRG downregulation of MBNL2 increases the expression of CCR2 in the DRG neurons and leads to CINP-like symptoms in naïve mice. Mechanistically, paclitaxel-induced downregulation of MBNL2 reduces its binding to the 3'-untranslated region of Ccr2 mRNA, thereby enhancing the stability of Ccr2 mRNA in the DRG. Given that MBNL2 and CCR2 are co-expressed in DRG neurons, these findings suggest that MBNL2 alleviates CINP, likely by destabilizing CCR2 expression in the DRG, and may represent a promising therapeutic strategy for this condition.

Disclosures: R. Ma: None. **Y. Tao:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.18/AA5

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH NS136138
NIH NS136108

Title: Nav1.5 in TrkB$^+$ Sensory Neurons Mediates Paclitaxel-Induced Mechanical Hypersensitivity

Authors: *A. PRUDENTE[1,2], B. LIMA ADJAFRE[3], S. LEE[2], S. D. DIB-HAJJ[4], S. G. WAXMAN[5], T. BERTA[2], T. M. CUNHA[6];
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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting and poorly managed toxicity of paclitaxel that severely affects patients' quality of life. However, the sensory neuron populations and ion channel mechanisms that sustain mechanical hypersensitivity remain incompletely defined. Classical nociceptors expressing Nav1.8 have been broadly implicated in pain processing, but their specific contribution to CIPN-associated allodynia is unclear. Here, we investigated whether Nav1.8$^+$ nociceptors or TrkB$^+$ low-threshold mechanoreceptors, as well as the non-canonical voltage-gated sodium channel Nav1.5 (*Scn5a/SCN5A*), play a role in paclitaxel-induced mechanical pain hypersensitivity. Using a mouse model of paclitaxel-induced CIPN (8 mg/kg, intraperitoneal injections on days 0, 2, 4, and 6) with von Frey behavioral testing, we first showed that mechanical hypersensitivity developed independently of Nav1.8$^+$ nociceptors. In contrast, chemogenetic silencing of TrkB$^+$ sensory neurons reversed paclitaxel-evoked allodynia, identifying this population as a critical mediator. Transcriptomic profiling of

TrkB$^+$ neurons revealed selective enrichment of *Scn5a* (Nav1.5) among voltage-gated sodium channel transcripts, a finding validated by reanalysis of published single-cell RNA-sequencing datasets and by in situ hybridization of mouse and human dorsal root ganglia tissues. Notably, *Scn5a* expression was upregulated in TrkB$^+$ neurons after paclitaxel treatment. To assess functional relevance, we performed siRNA-mediated *Scn5a* knockdown in primary sensory neurons, which significantly attenuated paclitaxel-induced mechanical hypersensitivity. Together, these results identify a previously unrecognized TrkB$^+$/Nav1.5 afferent axis as a key driver of CIPN and nominate Nav1.5 as a translationally relevant therapeutic target. These findings suggest that tissue-targeted strategies to inhibit Nav1.5 in mechanosensory neurons may offer a promising approach for alleviating CIPN.

Disclosures: A. Prudente: None. **B. Lima Adjafre:** None. **S. Lee:** None. **S.D. Dib-Hajj:** None. **S.G. Waxman:** None. **T. Berta:** None. **T.M. Cunha:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.19/AA6

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH NS045594
NS135157

Title: Targeted Sympathetic Denervation Relieves Cancer Bone Pain and Inhibits Tumor Progression in a Mouse Model of Bone Metastasis

Authors: *B. DA SILVA SOLEY, D. DENARDIN LÜCKEMEYER, W. XIE, J.-M. ZHANG; Univ. of Cincinnati, Cincinnati, OH

Abstract: Cancer-induced bone pain (CIBP) is a debilitating condition that severely impacts quality of life and currently lacks effective non-opioid therapeutic treatments. While peripheral nerves within the bone microenvironment are known to interact with cancer cells, the specific role of sympathetic signaling in driving CIBP and tumor progression remains unclear. To investigate this, we established a mouse model of metastatic breast cancer via intrafemoral injection of E0771 mammary carcinoma cells into female C57BL/6 mice. Our findings reveal that targeted sympathetic denervation at the L3/L4 level by surgical microsympathectomy (mSYMPX), performed either at the time of tumor inoculation (POD0) or after pain establishment (POD7), significantly reduced mechanical hypersensitivity and tactile allodynia, while improving spontaneous locomotor activity compared with tumor-bearing mice subjected to sham surgery. Furthermore, micro-CT analysis demonstrated that mSYMPX attenuated cancer-induced bone destruction. These physiological and structural improvements were accompanied by reduced intratumoral angiogenesis and a partial reversal of tumor-associated immunosuppression within the bone microenvironment. These findings demonstrate that

sympathetic signaling directly contributes to both pain hypersensitivity and tumor progression in metastatic bone disease, and that these effects are mediated by local sympathetic innervation rather than circulating catecholamines, suggesting that targeting peripheral sympathetic signaling represents a promising therapeutic strategy for simultaneously alleviating CIBP and limiting tumor growth. Supported by NIH/NINDS grants NIH NS045594 and NS135157.

Disclosures: B. da Silva Soley: None. **D. Denardin Lückemeyer:** None. **W. Xie:** None. **J. Zhang:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.20/AA7

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH T32GM108539 (AD)
NIH (HNA)
NIH (RG)

Title: Endometriosis lesions are preferentially innervated by hyperexcitable nociceptors associated with patient pain

Authors: *A. J. DOURSON[1], M. FLUEGEL[4], J. MWIRIGI[2], H. NAHMAN-AVERBUCH[3], R. W. GEREAU, IV[5];
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Abstract: Endometriosis pain is debilitating for many of the 10% of women affected by the disease, yet few studies evaluate the mechanisms underlying this chronic pelvic pain. Current treatments are often inadequate, necessitating surgical resection of endometrial-like lesions to manage symptoms. Unfortunately, lesions and pain often recur. Clinical studies suggest that lesion innervation, rather than disease stage, correlates with pain severity; however, the identity and functional properties of these lesion-innervating neurons remain undefined. We utilized a syngeneic mouse model of the disease to characterize dorsal root ganglia (DRG) sensory neurons that innervate peritoneal lesions or nearby control peritoneum. We found that these lesions are preferentially innervated by small-diameter, IB4-positive sensory neurons, suggesting neuronal growth factor receptor signaling. Patch clamp electrophysiology of lesion-innervating neurons revealed that these cells are hyperexcitable compared to size-matched control DRG neurons. To translate these findings, we performed proteomics of clinical lesion samples stratified by patient-reported pain. We identified an enrichment of many neurotrophic factors, including Glial Cell Line-Derived Neurotrophic Factor (GDNF), in lesions from patients who reported severe pain. GDNF aligned characteristically with the stroma of endometrial lesions, and its receptor, GFRα1,

expression levels correlated with levels of peripherin-positive axons. Histological analyses confirmed that stromal GDNF expression, as well as that of peripherin and GFRα1, is associated with clinical pain. These data provide functional evidence that lesions drive nociceptor excitability and implicate the stromal GDNF-GFRα1 signaling axis in the recruitment of nociceptors to lesions. Our results identify this axis and suggest that it may be a disease modifying target to provide novel, non-hormonal strategies for the management or recurrence of endometriosis pain.

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Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.21/AA8

Topic: E.01. Somatosensation – Pain and Itch

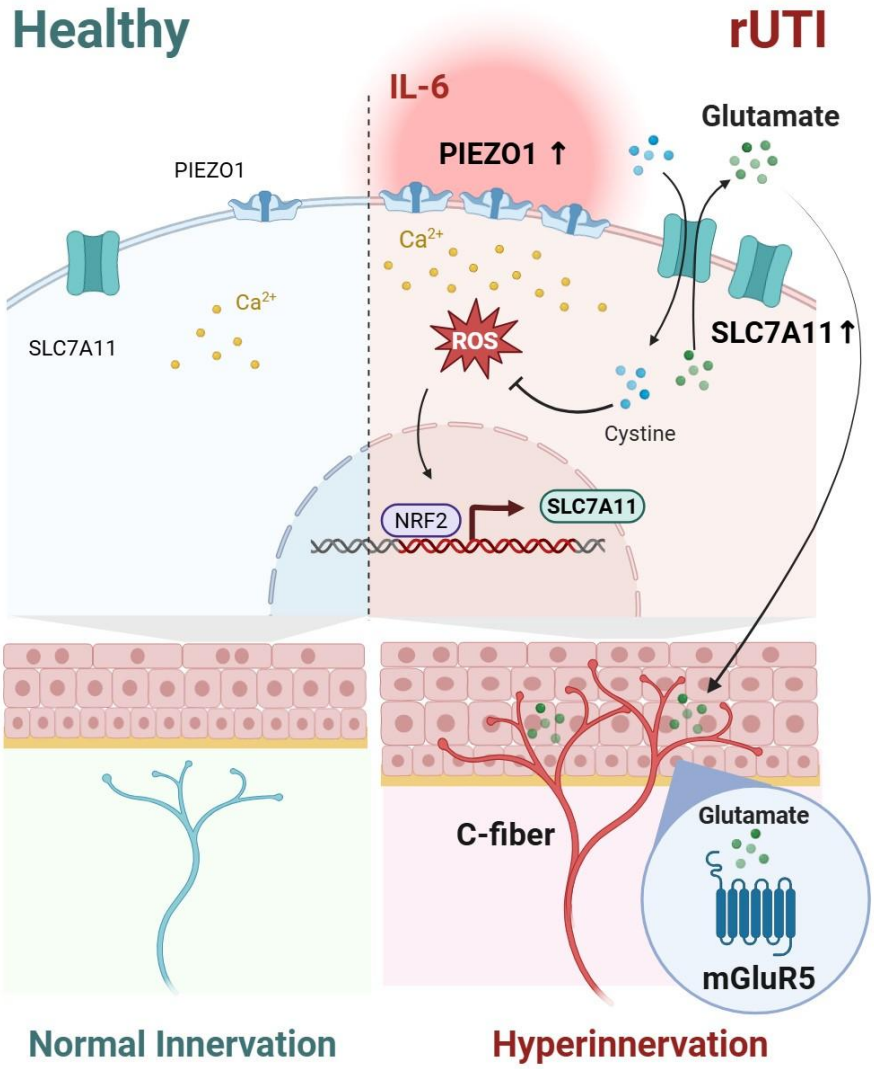
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Title: Excessive epithelial mechanosensation induces nociceptive remodeling and bladder pain through the PIEZO1-SLC7A11-Glutamate Axis

Authors: *M. KIM, B. LEE, H. CHOI;
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Abstract: Recurrent urinary tract infection (rUTI) is a major cause of chronic pelvic pain and voiding dysfunction, yet the mechanisms driving persistent sensory abnormalities remain poorly understood. Here, we identify a neuroepithelial signaling pathway that promotes nociceptive neuroplasticity during recurrent uropathogenic Escherichia coli (UPEC) infection. In mouse model, repeated UPEC infection led to persistent pelvic mechanical hypersensitivity, bladder overactivity, and extensive sprouting of peptidergic sensory fibers into the urothelium. Transcriptomic analyses revealed that repeated infections activate inflammatory pathways, including IL-6 signaling, which triggers upregulation of the mechanosensitive ion channel PIEZO1 in bladder epithelial cells via a STAT3 dependent pathway thus sensitizing epithelial cells to mechanical stimulation. PIEZO1-mediated Ca^{2+} influx promoted reactive oxygen species generation, activated NRF2-dependent antioxidant responses, and induced expression of the cystine-glutamate antiporter SLC7A11. Consequently, epithelial cells released elevated levels of glutamate, which stimulated neurite outgrowth and enhanced capsaicin responsiveness in

embryonic dorsal root ganglion neurons through mGluR5 signaling. In vivo, recurrent infection selectively increased CGRP-positive C-fiber remodeling within the bladder mucosa. Using urothelial-specific knockout mice (*Upk2Cre;Piezo1*$^{fl/fl}$ and *Upk2Cre;Slc7a11*$^{fl/fl}$), we confirmed that epithelial PIEZO1-SLC7A11 signaling is required for sensory hyperinnervation, pelvic hypersensitivity, and abnormal awake cystometric function following recurrent infection. . Pharmacological inhibition of SLC7A11 similarly reduced nociceptive remodeling and restored bladder function. Ultimately, these findings uncover an IL-6-PIEZO1-SLC7A11 signaling axis that bridges epithelial mechanical stress with chronic pain, presenting neuroepithelial glutamatergic signaling as a promising therapeutic target for rUTI-induced chronic bladder pain.



Disclosures: M. Kim: None. **B. Lee:** None. **H. Choi:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.22/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Title: Characterization of taxane-induced peripheral neuropathy in patients with breast cancer

Authors: A. CRISÓSTOMO JIMÉNEZ[1], I. I. RAMOS-RODRÍGUEZ[4], G. BAEZA-FLORES[2], *C. GUZMAN[3];
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Abstract: Taxane-induced peripheral neuropathy represents one of the most frequent dose-limiting toxicities in patients with breast cancer. In this context, taxanes constitute first-line agents employed in adjuvant and neoadjuvant regimens for this malignancy. It has been reported that 60-70% of patients treated with paclitaxel develop some degree of peripheral neuropathy during therapy, and in a considerable proportion of cases, symptoms persist for months or even years following treatment completion. This condition is clinically characterized by neuropathic pain, paresthesias, and allodynia, with a significant impact on quality of life and therapeutic continuity. Therefore, the present study aims to characterize taxane-induced peripheral neuropathy in patients with breast cancer, with the purpose of identifying the clinical and pharmacological factors associated with its onset and severity. The findings are expected to describe the predominant clinical profile of this complication in the studied population, as well as to identify the variables of greatest weight in its development. To this end, sociodemographic and clinical variables will be recorded, including cancer clinical stage, time elapsed since diagnosis, type of taxane administered, number of cycles received, dose per cycle, cumulative dose, infusion duration, use of premedication, and time elapsed from the last cycle to the moment of assessment. Additionally, comorbidities with independent neuropathogenic potential will be documented in order to control for their effect as confounding variables in the interpretation of results. Analysis of these variables is expected to enable the establishment of a preliminary predictive model that will contribute to the early detection and timely management of taxane-induced peripheral neuropathy in this population.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.23/AA9

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01 Grant CA263777
NIH R01 Grant CA241627

Title: Cancer-derived extracellular vesicles contribute to bone cancer pain and nociceptor sensitization by altering outward potassium leak currents (K2P).

Authors: V. VIATCHENKO-KARPINSKI[1], L. NEAL[2], E. ZHAO[1], R. MOHAMMED[1], I. A. KHASABOVA[1], D. A. SIMONE[1], *S. G. KHASABOV[1];
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Abstract: Pain is among the most debilitating symptoms of primary and metastatic bone cancer, yet the mechanisms of cancer-induced bone pain (CIBP) are not fully understood. Using our established model of bone cancer pain, produced by implantation of fibrosarcoma cells in and around the calcaneus bone, we showed earlier that tumor growth caused sensitization of nociceptors, and this occurred, in part, through the release of extracellular vesicles (EVs) from the cancer cells. However, the underlying biophysical mechanisms by which nociceptors become sensitized are not known. We therefore conducted electrophysiological studies *in vitro* to determine changes in membrane properties of nociceptive dorsal root ganglia (DRG) neurons that contribute to cancer-evoked sensitization. Fibrosarcoma cells implantation induced sex independent unilateral hyperalgesia and ongoing CIBP. To determine how CIBP alters intrinsic membrane properties of primary afferents, we performed whole-cell patch-clamp recordings from nociceptive neurons isolated from L3-L5 dorsal root ganglia (DRG). Nociceptors innervating the tumor-bearing area were retrogradely labeled by injection of DiI into the plantar hindpaw before tumor implantation. DiI-labeled nociceptors from naïve mice served as controls.Nociceptors from mice with CIBP exhibited membrane depolarization (-57.4±1.37 vs. -67.7±1.78 mV in controls) and reduced rheobase (61.2±6.96 vs. 218.8±37.98 pA), indicating increased excitability. These changes resulted from suppression of outward potassium leak currents mediated by K2P channels. In tumor-bearing mice, K2P current density at +1.7 mV was reduced by ~60% (8.9±1.16 vs. 24.1±2.87 pA/pF in controls), whereas voltage-gated inward and outward currents were unchanged. We next examined whether cancer EVs alter membrane properties of nociceptors in naïve mice. Superfusion of cancer EVs reduced K2P currents by ~50%, producing membrane depolarization and hyperexcitability similar to that observed in neurons from mice with CIBP. Control EVs from fibroblasts had no effect. Voltage-gated inward and outward currents remained unchanged. These findings identify suppression of K2P-mediated leak conductance as a major mechanism underlying nociceptor hyperexcitability during bone cancer and demonstrate that tumor-derived EVs directly contribute to this process. Targeting EV-dependent suppression of K2P currents may provide a novel therapeutic strategy for bone cancer pain.

Disclosures: V. Viatchenko-Karpinski: None. **L. Neal:** None. **E. Zhao:** None. **R. Mohammed:** None. **I.A. Khasabova:** None. **D.A. Simone:** None. **S.G. Khasabov:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.24/AA10

Topic: E.01. Somatosensation – Pain and Itch

Support: NSERC Grant
CFI Grant

Title: A single exposure to predator threat induces persistent hyperalgesia following CFA-induced inflammatory injury in adult male Sprague-Dawley rats

Authors: *B. R. O'BRIEN[1], H. LEHMANN[2], L. J. MARTIN[4], N. M. FOURNIER[3]; [2]Psychology, [3]Dept. of Psychology, [1]Trent Univ., Peterborough, ON, Canada; [4]Psychology, Univ. of Toronto, Mississauga, ON, Canada

Abstract: Pain represents an internal state that can heighten an animal's sensitivity to environmental threat. Previous work in mice showed that inflammatory injury induced by complete Freund's adjuvant (CFA) amplifies defensive freezing evoked by trimethylthiazoline (TMT), a synthetic predator odorant associated with fox urine and feces. CFA-primed mice exposed to TMT also developed prolonged mechanical hypersensitivity, measured using von Frey filaments, which was reversed by the corticosterone synthesis inhibitor metyrapone. These findings suggest that predator threat following injury can induce long-lasting sensitization within stress and pain circuits. Here, we examined whether persistent pain-related sensitization could be replicated in rats and whether stress exposure or neuroendocrine activation alone was sufficient to drive this sensitized state. Across three experiments, adult male Sprague-Dawley rats were primed with intraplantar CFA (25%; total N = 80) and exposed 24 h later to TMT, corticosterone (10 mg/kg, i.p.), 30 min elevated platform stress, 5 min live predator exposure (barn owl), or no-stress control conditions. Mechanical withdrawal thresholds were assessed with von Frey filaments across multiple post-injury time points. Previous work in our laboratory showed that brief TMT exposure after CFA produced persistent ipsilateral mechanical hypersensitivity lasting at least 3 months. In the present experiments, all CFA-primed groups showed reduced ipsilateral withdrawal thresholds within 72 h. However, thresholds returned to baseline by Days 10-14 in rats exposed to corticosterone, elevated platform stress, or no-stress control conditions. In contrast, live predator exposure 24 h after CFA produced persistent ipsilateral hypersensitivity comparable to the TMT effect, but also produced delayed contralateral sensitization that was not observed following TMT exposure. Together, these findings indicate that neuroendocrine activation alone is insufficient to produce persistent pain-related sensitization. Instead, ecologically relevant predator threat may be a key driver of long-lasting plasticity within interacting stress and pain systems following inflammatory injury.

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Poster

PSTR056: Pain: Peripheral Mechanisms

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Program #/Poster #: PSTR056.25/AA11

Topic: E.01. Somatosensation – Pain and Itch

Support: R16GM153601
P30GM145497

Title: Categorizing Cell Types Expressing ATF3 in a Model of Knee Joint Osteoarthritis

Authors: *J. HOWARD[1], A. DEL GRECO[2], P. CARADONNA[2], T. E. KING[3];
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Abstract: Knee joint osteoarthritis (KJOA) is becoming increasingly prevalent due to aging populations and rising obesity rates. Current treatment strategies are cost prohibitive and ineffective for many patients. KJOA is characterized by evoked pain, brought on by joint use, and constant pain that does not dissipate with rest. A lack of mechanistic knowledge underlying phenotypically distinct pain states have hindered the development of effective treatments for OA pain. The murine model of monosodium iodoacetate (MIA)-induced KJOA pain demonstrated that mice with constant pain have elevated ATF3 RNA, a marker of nerve injury, in L2-L5 dorsal root ganglia (DRGs). In contrast, mice with joint use pain without constant pain do not. This model was used to explore cell and tissue specific expression of ATF3 protein in the ipsilateral L2-L4 DRGs of male mice. Constant pain was identified in mice by conditioned place preference to analgesia while joint use pain was measured using weight asymmetry. Following behavioral analyses, dorsal root ganglia (DRGs) were collected, whole mounted, and stained for ATF3 (activating transcription factor 3) and CGRP (calcitonin gene-related peptide). Quantitative analysis showed that ATF3 expression was increased in L2 and L3 DRGs selectively in mice with MIA-induced constant joint pain. Higher levels of ATF3 expression were observed in L2 compared to L3 DRGs. No change in co-localization of ATF3 with CGRP was observed. These data demonstrate that ATF3 expression is induced in DRGs associated with the knee joint, but that this is not in CGRP expressing neurons. Characterization of ATF3 expression using molecular markers of other sensory neuron populations and immune cell populations is ongoing. This work was supported by R16GM153601 and P30GM145497.

Disclosures: J. Howard: None. **A. Del Greco:** None. **P. Caradonna:** None. **T.E. King:** None.

Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.26/AA12

Topic: E.01. Somatosensation – Pain and Itch

Support: R16GM153601
P30GM145497

Title: FOS expression along the ascending pain pathway in mice with or without constant osteoarthritis pain

Authors: T. FLANAGAN, A. DEL GRECO, H. NASSER, T. CHIN, P. CARADONNA, ***T. E. KING**;
Univ. of New England, Biddeford, ME

Abstract: Osteoarthritis (OA) pain is a leading cause of chronic musculoskeletal pain. A significant barrier to pain management is the heterogeneous nature of OA pain. Some OA patients report joint use pain that abates with rest. Others develop constant joint pain that does not abate with rest. There is limited understanding of mechanisms underlying transition from intermittent joint use pain to constant pain that fails dissipate with rest. Using the monosodium iodoacetate (MIA) model of knee joint OA in mice, we have characterized concentrations that evoke joint use pain with or without constant pain. Following behavioral analyses, we collected spinal cords and brains and performed whole tissue clearing and staining for FOS, an early oncogene marker used to detect neural activity. Analysis of FOS expression along the ascending pain pathway including the spinal cord, lateral parabrachial nucleus, and medial thalamus was performed using IMARIS software. The ipsilateral spinal dorsal horn had increased FOS expression in mice with constant joint pain compared to their contralateral dorsal horn and compared to saline controls. More specifically, increase FOS expression was observed in lamina 3, 4 and 5 indicating increased FOS in the deep dorsal horn. A significant increase in FOS expression was also observed in the ipsi- and contralateral LPBN of mice with constant joint pain compared to saline controls. Similarly, significantly elevated FOS expression was observed in the medial thalamus of mice with constant joint pain compared to saline controls. Mice with joint use pain in the absence of constant pain failed to demonstrate significant increases in FOS expression across any of these regions compared to saline controls. Overall, these observations indicate ongoing activity along the ascending pain pathway is selectively observed in mice with constant pain indicating ongoing nociceptive drive in the context of constant pain. Future studies are planned to determine cell types and circuits along this pathway implicated in maintaining constant joint pain. This work was supported by R16GM153601 and P30 GM145497.

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Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.27/AA13

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R16GM153601
NIH P30GM145497

Title: Mapping OA Pain: Machine Learning and Biomarkers Reveal the Roots of Constant vs. Intermittent Joint Pain

Authors: *A. DEL GRECO[1], T. FLANAGAN[1], J. HOWARD[3], P. CARADONNA[1], T. E. KING[2];
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Abstract: Osteoarthritis (OA) treatments are limited by pain heterogeneity; some patients experience pain only during joint use, while others suffer from constant pain. The mechanisms driving these distinct clinical phenotypes remain poorly understood, creating a significant barrier to drug development. To model these phenotypes, OA was induced in mice via intra-articular monosodium-iodoacetate (MIA) injections at concentrations generating either joint-use pain alone or joint-use pain combined with constant pain. Posture and behavior were evaluated using static weight-bearing, climbing assays, and machine-learning-based BlackBox video analysis. Tissues were then analyzed for nerve injury (ATF3) in L2-L5 dorsal root ganglia (DRGs) and neuronal activity (FOS expression) in the lateral parabrachial nucleus and medial thalamus. Mice with constant pain exhibited elevated ATF3 in L2 DRGs and increased FOS expression in both brain regions, whereas mice with joint-use pain alone mirrored saline controls. Principal component analysis (PCA) revealed that altered postures (weight asymmetry), behaviors (hindpaw lifting) and reduced mobility (distance moved, climbing time) strongly and negatively correlated with both FOS and ATF3 expression. These data successfully bridge behavioral readouts with biomarkers of nerve injury and activity in the ascending pain pathway. These data indicate that there are distinct patterns of behavioral and postural changes that correspond to neuroplastic changes in the peripheral and central nociceptive pathway in a pain dependent manner in OA joint pain. This work was supported by R16GM153601 and P30GM145497.

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Poster

PSTR056: Pain: Peripheral Mechanisms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR056.28/AA14

Topic: E.02. Somatosensation – Touch

Support: Fulbright U.S. Student Program

Title: Serum Neurofilament Light Chain and Self-Reported Neuropathic Symptom Burden in a Ghanaian Community Sample

Authors: I. MULLINGS[1], P. ZIGLI[2], J. K. ADASE[3], A. NISANMAN[3], S. BOAKYE GYAN OPPONG[3], E. NTIM[7], L. AMPONSAH[3], S. AMOAH[4], D. L. EGBENYA[5], ***F. T. DJANKPA**[6]; [1]Dept. of Psychology, Fordham Univ., Bronx, NY; [2]Dept. of Physiol., Univ. of Cape Coast, Accra, Ghana; [3]Dept. of Physiol., Univ. of Cape Coast, Cape Coast, Ghana; [4]Anat. and Cell Biol., Univ. of Cape Coast, CAPE COAST, Ghana; [5]Dept. of Physiol., Univ. of Cape Coast, University of Cape Coast, Ghana; [6]Univ. of Cape Coast, Cape Coast, Ghana; [7]Dept. of Physiol., Kwame Nkrumah Univ. of Sci. and Technol., Kumasi, Ghana

Abstract: Serum neurofilament light chain (sNfL) is an emerging blood biomarker of neuro-axonal injury. Its utility for detecting neuropathy symptoms in community settings and the extent to which local environmental or contextual factors influence sNfL is not well characterized, particularly in sub-Saharan Africa. We therefore measured sNfL and examined its relationship with self-reported neuropathic symptom burden and other demographic, clinical and environmental factors in a community sample in Ghana. In this cross-sectional study, we recruited adults from six Ghanaian communities: Adjuboe (E/R), Beposo (A/R), Cape Coast Metropolis (C/R), Dunkwa Offin (C/R), Twifo Darmang (C/R) and Vume (V/R). Venous serum NFL was quantified by ELISA and log-transformed for analysis. Neuropathy symptom burden was captured using a simple symptom checklist and summarized as a symptom count. Participants were classified as Asymptomatic (score = 0) or Symptomatic (score ≥1). Descriptive statistics, Wilcoxon tests, Spearman correlation, receiver operating characteristics (ROC) analysis, and linear regression (univariate and multivariable) were used to evaluate associations between log NFL and covariates. Analyses were performed on complete cases (N = 134). The analytic sample included 134 participants (Asymptomatic n = 52; Symptomatic n = 82). Symptomatic participants were older (median age 46.5 years, IQR = 33-62 years) than asymptomatic participants (median age 22.5 years, IQR = 19-28 years; $p < 0.001$). Median serum NfL was higher in Symptomatic versus Asymptomatic participants (60.6, IQR=31.8-96.5 pg/mL vs 25.1, IQR= 0.7-53.3 pg/mL, $p < 0.001$). Log NfL correlated moderately with neuropathy symptom score (Spearman $\rho = 0.395$, 95% CI 0.237-0.543) and with age ($\rho = 0.406$, 95% CI 0.250-0.558). On ROC analysis, log-transformed NfL discriminated symptomatic from asymptomatic participants with an AUC of 0.730 (95% CI 0.632-0.814), indicating fair-to-good discrimination. In univariable linear models, neuropathy symptom score, age, untreated water source, and chronic disease were each associated with higher log NfL. In the primary multivariable model, however, neuropathy symptom score was no longer independently associated with log NfL ($\beta = -0.003$, 95% CI −0.237 to 0.242; $p = 0.982$) while community location, notably residence in Cape Coast, remained an independent correlate ($\beta = -1.823$, 95% CI −2.995 − 0.651; $p < 0.003$). In conclusion, sNfL was higher among participants reporting neuropathic symptoms and demonstrated fair discrimination for symptomatic status, but the symptom-sNfL association was substantially attenuated after adjustment for contextual factors.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.01/Web Only

Topic: E.02. Somatosensation – Touch

Support: JSPS KAKENHI (22K18263)

Title: Electrocorticographic activity associated with the cutaneous rabbit effect: A case study

Authors: *M. HAKAMATA[1], N. KAWAGUCHI[2], K. TAKAMA[1], M. MIYAZAKI[3,1];
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Abstract: The cutaneous rabbit effect (CRE) is a tactile illusion that reveals postdiction, in which the perceived position of an earlier stimulus is attracted toward a later stimulus. A previous study using functional magnetic resonance imaging (fMRI) demonstrated CRE-related activity in a region with receptive fields located at the illusory sensation site in the primary somatosensory cortex (S1). However, the temporal dynamics of the CRE-related neural activity have remained unclear. In this study, we measured neural activity during the CRE using electrocorticography (ECoG), which has high temporal and spatial resolutions. One person with epilepsy participated in this study. Electrodes were implanted over the patient's right hemisphere for presurgical evaluation. For each trial, three sequential taps were presented on the participant's forearm to induce the CRE. The first tap was a reference stimulus, which was constantly presented 800 ms before the second tap. The second and third taps were the attractee and attractor stimuli, respectively, and the inter-stimulus interval (ISI) was 50, 200, or 800 ms. At the end of each trial, the participant reported the perceived positions of the taps. The participant exhibited the CRE even in trials with long ISIs (200 and 800 ms), although the CRE typically occurs with ISIs shorter than 200 ms in previous studies with healthy participants. We analyzed the ECoG signals in trials with an ISI of 800 ms, in which the CRE was reported in approximately half of the trials. We first classified trials into those in which the CRE was perceived (CRE trials) and those in which it was not (non-CRE trials). Then, using Morlet wavelets, we computed the time-frequency power of the ECoG signals and compared it between the CRE and non-CRE trials. As a result, in the ECoG signals from two adjacent electrodes located around S1, significantly greater power was found in the CRE trials. The power increase extended approximately 600 ms after the attractee stimulus and was found in the gamma band (60-80 Hz). The CRE-related increase in power may reflect a neuronal state associated with subsequent postdictive modulation of perception.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.02/AA15

Topic: E.02. Somatosensation – Touch

Support: NWO Grant 024.005.022

Title: Active Scanning of Artificial Textures Reveals Cortical Encoding of Surface Spectral Properties

Authors: *I. KYRIAZIS[1], M. TER WAL[1], A. C. SCHOUTEN[3], F. C. VAN DER HELM[1], M. VAN DE RUIT[2];
[1]Biomechanical Engin., [2]Dept. of Biomechanical Engin., Delft Univ. of Technol., Delft, Netherlands; [3]Biomechanical Engin., Delft Univ. Tech., Delft, Netherlands

Abstract: Active touch depends on continuous tactile feedback and results in cortical rhythmic activity that informs about the properties of touch stimuli. Based on this, we hypothesized that cortical activity during active texture exploration encodes spectral properties of tactile stimuli when scanning velocity is held constant. If this relationship holds, neural rhythms carry structured information about texture features rather than merely reflecting general levels of activity. Understanding the neural rhythms associated with touch is important for the development of haptic technologies, tactile BCIs, and sensory feedback systems for prosthetic devices. Fifteen healthy participants (7 female) actively scanned four 3D-printed surfaces while 128-channel electroencephalography (EEG) was recorded. Textures consisted of: a single-frequency pattern corresponding to 23 Hz at a scanning velocity of 50 mm/s, a triplet-frequency pattern containing 17, 23, and 29 Hz components, a multisine texture spanning 1 to 40 Hz, and a flat control surface. Participants were guided to maintain constant scanning velocity using a blinking LED without visual feedback of hand movement. EEG data were analyzed using the grouped spectral densities, and source-space activity was reconstructed using eLORETA. Statistical significance was assessed using t-tests with FDR correction. Scanning surfaces elicited distinct cortical responses compared to the flat control. Group-level analyses over contralateral sensorimotor electrodes (CP3) revealed significant alpha and low beta desynchronization followed by high beta and gamma synchronization during scanning ($p < 0.05$). In contrast, the flat surface produced only desynchronization effects. Distinct textures generated separable spectral response patterns corresponding to the temporal frequencies induced by scanning velocity. The single-frequency texture also evoked stronger gamma-band synchronization than multi-frequency textures, potentially reflecting enhanced cortical processing of temporally predictable tactile input. At source level, the motor and primary sensory regions were found to produce the most activity, with frontal components emerging as time progressed. Behavioral reports indicated that participants could discriminate between the flat and single sine, but confused the triplet and multisine more often. Together, these findings demonstrate that cortical oscillatory dynamics during active touch retain information about the frequency composition of tactile textures under natural scanning conditions.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.03/AA16

Topic: E.02. Somatosensation – Touch

Support: We thank the participants who took part in our experiment. We are grateful to Gilles Vannuscorps and Alfonso Caramazza for providing and contributing to the Harvard dataset that supported part of the analyses reported here. This work was supported by

Title: Global remapping in SI in people born without hands

Authors: *F. TAHERIYAN[1], Z. DENG[1], M. CZARNECKA[1], F. A. MARTINEZ-ADDIEGO[1], Y. LIU[2], E. STRIEM-AMIT[1];
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Abstract: How congenital handlessness reshapes cortical body maps remains a question in brain plasticity. It was long assumed that the face area overtook the missing hand territory in the primary somatosensory cortex (SI) after arm amputation. However, recent evidence suggests that the cortical body map remains stable after acquired limb loss. Can large-scale cortical reorganization between the SI hand area and neighboring areas occur following congenital handlessness? To test this, we recorded fMRI data from 17 typically developed individuals (TDs) and 8 individuals with upper-limb dysplasia (IDs) while they performed movements of the mouth, shoulder, abdomen, and foot. TDs additionally performed hand movements. We calculated the center of gravity (COG) of each body part's responses along the lateral-to-medial somatotopic axis of SI on the cortical surface.Our results show that, in IDs, the center of gravity of the shoulder, abdomen, and foot representations shifted toward the hand region, from the superior-medial toward the inferolateral portions of SI. In contrast, mouth responses did not shift toward the hand area in IDs. These results were replicated using individual peak response analysis: shoulder and abdomen peaks shifted in IDs, but the mouth did not. Together, these findings suggest that large-scale SI reorganization can occur in congenital bilateral hand absence, but that the face-hand border may constrain remapping even following such early-onset and complete sensorimotor deprivation.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.04/AA17

Topic: E.02. Somatosensation – Touch

Support: 4-VA Collaborative Research Grant

Title: Motor activation magnitude, rather than the arm activated, determines sensorimotor gating during bimanual tactile stimulation

Authors: N. KALANTARYARDEBILY[1], M. AHRENS[2], J. M. YAU[3], A. PAUL[4], ***N. GURARI**[1];
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Abstract: Voluntary movement suppresses perception of externally applied tactile stimuli in the moving limb (sensorimotor gating). Prior work primarily tested gating with unilateral tactile input. How gating scales with motor activation during bimanual tactile input—which better reflects everyday bimanual arm use—remains unclear. We tested whether scaled unilateral or bilateral elbow flexion modulates left-finger detection thresholds during concurrent bimanual stimulation. Participants completed a tactile detection task using two up-down staircases at the left fingertip to obtain average detection thresholds. Throughout, right-fingertip stimuli were fixed at two times each participant's right-hand detection threshold, providing constant suprathreshold contralateral input. Seven conditions were randomly presented, consisting of isometric elbow flexion at 0%, 25%, or 50% maximum voluntary torque (MVT) performed with the left arm (ipsilateral activation), right arm (contralateral activation), or both arms (bilateral activation). Elbow flexion was enforced via real-time audiovisual feedback, and trial timing, including rest breaks, was paced by audio cues. We modeled the change in left-finger detection threshold relative to 0% MVT using a linear mixed-effects model with activated arm (ipsilateral, contralateral, bilateral) and activation level (25% vs 50% MVT) as fixed factors and participant as a random factor; an analysis of variance identified significant effects. Twelve adults with no musculoskeletal or neurological injury participated (age range 41-75, median 61; 8 female, 4 male). Detection thresholds increased significantly with activation level ($\chi^2(1) = 25.6$, $p < 0.001$), relative to the 0% MVT baseline. Estimated mean change was negligible at 25% MVT (≈0 mA), but increased by 0.535 mA at 50% MVT. The main effect of activated arm did not reach significance ($\chi^2(2) = 5.66$, $p = 0.059$), and there was no activated arm × activation level interaction ($\chi^2(2) = 1.00$, $p = 0.607$). These findings demonstrate that sensorimotor gating during concurrent bimanual stimulation is modulated by the magnitude of voluntary motor activation. The absence of an interaction between the arm activated and activation level suggests that this effect is consistent across ipsilateral, contralateral, and bilateral activation conditions. Together, these results indicate that the degree to which the arm is activated, rather than the specific arm activated, is the primary determinant of tactile suppression during concurrent bimanual stimulation.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

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Topic: E.02. Somatosensation – Touch

Support: NIH grant R01NS129982

Title: Interhemispheric modulation of neuron responses in area 3b cortex in monkeys with and without spinal cord lesions

Authors: *J. L. REED[1], H. QI[2], J. H. KAAS[3];
[2]Dept Psychol, [3]Psychology Dept., [1]Vanderbilt Univ., Nashville, TN

Abstract: Studies of primary somatosensory cortex area 3b reveal neuron response modulation when a site inside the receptive field (RF) is stimulated alongside a site outside the RF, including the opposite hand. The hand representation in primates is unique in that there are very few, if any, callosal connections between hemispheres for left and right area 3b. When stimuli are presented to both hands, the term interhemispheric modulation is used because each hemisphere of cortex represents the opposite hand in area 3b. When we refer to neurons that show interhemispheric modulation, we use the term extra-hand RF. Our goal is to determine the sources and properties of the extra-hand RF. We used multichannel arrays to record from area 3b in adult squirrel monkeys (*Saimiri boliviensis*, *S. sciureus*, n = 2, 1 female) and owl monkeys (*Aotus trivirgatus*, *A. azarae*, n = 6, 3 female) without lesions and those after at least 9 weeks of recovery after unilateral dorsal column lesions (*S. sciureus*, n = 2, 1 female; *A. trivirgatus*, n = 4, 2 female). We expected that dorsal column lesions would affect the proportions of inhibitory neurons responsive to stimuli on both hands. Characteristics of extracellular recordings were used to classify neuronal signals as regular spiking units (RSU), putative excitatory neurons, and fast spiking units (FSU), putative inhibitory neurons, to evaluate responses to surround stimulation. Spike signals were acquired and timed to computer-controlled indentations to the skin on selected sites. Stimuli were presented to one spot on the hand, or stimuli were paired and presented to matched or unmatched sites on both hands. When sites on one or both hands were stimulated simultaneously or asynchronously, neurons in the affected area 3b of monkeys with dorsal column lesions and neurons in area 3b of normal monkeys showed response magnitude suppression, no change, or facilitation. Interhemispheric modulation occurs throughout the cortical column, with minimal differences in the proportions of inhibitory and excitatory responses in FSU and RSU neurons recorded from monkeys with and without unilateral dorsal column lesions (paired t test $p = 0.61$), and minimal differences in latency (paired t test $p = 0.68$). These findings support our evidence that there are both cortical and subcortical contributions to the extra-hand RF in area 3b.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.06/AA18

Topic: E.02. Somatosensation – Touch

Support: NHMRC Ideas Grant GNT2003646
NHMRC Fellowship GNT1106370

Title: Layer 5 corticothalamic-recipient neurons in higher-order thalamus dynamically encode perceptual learning

Authors: W. ZHANG[1], R. DINGWALL[2], ***C. MO**[2];
[1]Anat. and Physiol., The Univ. of Melbourne, Melbourne, Australia; [2]The Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Perceptual learning involves experience-dependent changes in distributed neural circuits. While layer 5 corticothalamic projections are increasingly implicated in perception and learning, how these inputs shape activity within higher-order thalamus during learning remains poorly understood.
Here, we longitudinally monitored primary somatosensory cortex layer 5 (S1 L5)-recipient neurons in the posterior medial thalamus (POm) throughout acquisition of a whisker-based texture discrimination task. We combined optogenetic tagging of S1 L5 terminals (ChrimsonR) with 1-photon miniscope calcium imaging (GCaMP6m) in POm, enabling identification of S1 L5-recipient and non-tagged POm neurons within the same field of view. Mice were trained on a go/no-go texture discrimination task incorporating a delay period (0.5 s) between sensory and response epochs.
Compared with non-tagged POm neurons, S1 L5-recipient POm neurons exhibited progressive changes in task-related activity as animals transitioned from naive to expert performance. These changes included enhanced separation of rewarded and unrewarded stimulus population response during sensory and delay periods, suggesting learning-dependent refinement of task representations within corticothalamic-recipient ensembles. Population clustering analyses further revealed diverse functional subpopulations within POm that shifted in prevalence and response properties across learning.
Ongoing reversal-learning and linear modelling analyses aim to further dissociate sensory, motor, and outcome-related signals within these identified POm subpopulations.
Together, these findings demonstrate learning-dependent reorganisation of activity within corticothalamic-recipient higher-order thalamic circuits and support an emerging role for higher-order thalamocortical networks in adaptive behaviour and perceptual learning.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.07/AA19

Topic: E.02. Somatosensation – Touch

Support: NSF GRFP, DGE-20

Title: The role of local thalamic interneurons in thalamocortical network stability

Authors: *T. K. RAMIREZ[1], C. D. MAKINSON[2];
[1]Neurol., Columbia Univ., New York, NY; [2]Neurol., Columbia University, Irving Med. Ctr., New York, NY

Abstract: Hyperexcitability within the somatosensory thalamocortical circuit can drive spike-and-wave discharges (SWD) that define absence seizures[1,2]. Reducing the $GABA_A$ receptor β3 subunit (Gabrb3) intensifies oscillatory synchrony within this circuit[3]. Findings support the idea that recurrent inhibition within the thalamic reticular nucleus (TRN-TRN inhibition) acts as a desynchronizing brake in the thalamocortical rhythm generator[3,4,5]. These findings rest on the explicit assumption that the TRN is the only significant source of inhibitory control in the rodent somatosensory thalamus, yet adult TRN-TRN connections are rare[6,7,8]. Recent work, however, has identified local inhibitory cells (VPis) as another notable source of inhibition within the somatosensory thalamus[9,10,11,12,13]. VPis make up only 1-4% of neurons in the mouse somatosensory thalamus, yet one VPI can span 800μm, encompassing the full breadth of the VP. They release vesicles dendritically, and their extensive dendritic branching allows each VPi to impact hundreds of thalamocortical relay cells. VPis migrate into the VP postnatally, plateauing at around 2 weeks of age[14,15,16]. This developmental timing coincides with the reduction of intra-TRN inhibition, raising the possibility that VPis may play an important role in the control of thalamic networks later in development. To address this hypothesis, we generated conditional knockout Gabrb3 animals with cell type-specific loss of Gabrb3 in either TRN cells or VPis and measured the resulting SWD burden. We measured cortical and thalamic activity *in vivo* using EEG and fiberphotometry and observed that Gabrb3 knockout in VPi neurons is sufficient to produce SWDs. Using an acute thalamic slice preparation that maintains local thalamic circuitry, we found that Gabrb3 knockout in VPi neurons enhanced thalamic network bursting activity *ex vivo*. Together, these findings suggest that VP interneurons help regulate thalamocortical oscillatory activity in adulthood.

Disclosures: T.K. Ramirez: None. **C.D. Makinson:** None.

Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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Topic: E.02. Somatosensation – Touch

Support: Electronics and Telecommunications Research Institute (ETRI) grant funded by the Korean government (No. 26ZB1330)
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Title: Peripheral electrical microstimulation and mechanical pressure recruit overlapping recorded populations in mouse ventral posterolateral thalamus

Authors: *J. KIM[1], S. PARK[1], K.-H. PARK[1], G. LEE[2], Y. CHOI[2], S. JUNG[2];
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Abstract: The ventral posterolateral (VPL) thalamus relays somatosensory signals, but how it responds to peripheral electrical microstimulation versus graded sustained pressure—and whether these inputs engage shared circuitry—remains unclear. In urethane-anesthetized male C57BL/6 mice (8-12 weeks), we recorded VPL-region wideband extracellular activity with 16-channel Nitinol microelectrode arrays and extracted multi-unit spikes during biphasic, charge-balanced peripheral microstimulation (100 μs/phase; n = 7) and graded von Frey pressure (0.1-300 mN; n = 6), applying an identical pipeline across inputs. Controlling stimulation artifact was a necessary first step, because it critically altered inferred firing. In ungrounded recordings, pulse-locked deflections near stimulation pulses were enriched up to 19-fold above chance, were synchronous across channels, and could pass waveform-correlation criteria, so template matching alone was insufficient to reject them. A subcutaneous active ground with common-average referencing yielded artifact-controlled recordings; ungrounded sessions were excluded. In artifact-controlled data, microstimulation evoked excitatory responses with first-spike latency of 11-12 ms and reliable pulse-locked following, whereas contaminated sessions instead showed apparent suppression. At sites defined as responsive, the evoked rate rose ~3 Hz above pre-stimulus baseline (~37-48% of natural vibrotactile drive at matched frequencies)—a responsive-site conditional measure that was modest at the population level. Within the artifact-controlled cohort, site-wise response magnitudes to pressure and to microstimulation were correlated (Spearman ρ ~+0.5 to +0.6), indicating overlapping rather than disjoint input representations, though substantial unshared variance remained. Sustained von Frey pressure modulated VPL multi-unit firing. Pooled across animals, activity increased with force (~100-180 spikes/s over 0.1-300 mN), but per-animal gain and response direction were heterogeneous, so the pooled trend should be read cautiously. Because von Frey stimuli were hand-applied without electronic onset triggers, only sustained rate was analyzed. Together, sustained pressure and peripheral microstimulation recruited overlapping recorded populations in VPL-region thalamus. Once artifact was controlled, microstimulation produced touch-like excitation, while pressure revealed

force-dependent but animal-specific modulation—supporting artifact-aware analysis and biologically grounded thalamic stimulation design.

Disclosures: J. Kim: None. **S. Park:** None. **K. Park:** None. **G. Lee:** None. **Y. Choi:** None. **S. Jung:** None.

Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.09/AA21

Topic: E.02. Somatosensation – Touch

Support: NIH Grant ZIAMH002959

Title: Modulation of local network dynamics by behavioral state-sensitive neurons in primary somatosensory cortex

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Abstract: Individual cortical neurons are highly heterogeneous in their functional properties. Even in primary somatosensory cortex, where activity is often studied in relation to sensory inputs, many neurons are strongly associated with behavioral state, including spontaneous movement. While neural activity related to behavioral state is widespread across the brain, its function in local cortical circuits is still poorly understood. A key unresolved question is whether these neurons simply reflect ongoing behavioral state or actively shape local network dynamics. To address this, we combined two-photon calcium imaging with holographic optogenetic stimulation in awake, head-fixed mice. We recorded activity from large populations of neurons in superficial layers of primary somatosensory cortex during spontaneous movement and whisker stimulation, and classified neurons as locomotion-related, sensory-related, or neither based on their activity patterns. We then selectively stimulated neurons from each functional group while monitoring responses in the local network across different behavioral conditions, including spontaneous movement and stationary states, with or without whisker stimulation. Preliminary results showed that stimulation of each group induced both excitation and suppression in non-target neurons, with suppression predominating at the population level. Locomotion-related neurons preferentially excited other locomotion-related neurons. In contrast, stimulation of sensory-related neurons produced stronger suppression in other sensory-related neurons. In addition, locomotion-related neurons suppressed sensory-related neurons. These findings suggest that behavioral state-related neurons in primary somatosensory cortex may contribute to local network dynamics through distinct interactions among locomotion- and sensory-related ensembles.

Disclosures: L. Zhang: None. **M. Han:** None. **A. Inacio:** None. **S. Lee:** None.

Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.10/AA22

Topic: E.02. Somatosensation – Touch

Support: NIBIB R01EB029857
NIBIB T32EB025816
NINDS RF1NS128896

Title: Cortical and thalamic excitability independently shape sensory detection by tuning spontaneous and sensory-evoked activity

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Abstract: Thalamocortical excitability shapes sensory processing and perception, yet how changes in the excitability across thalamus and cortex affect behavior, network activity, and sensory encoding remains unclear. Here, we directly tested how the excitability of the mouse primary somatosensory cortex (S1) and the corresponding first-order thalamic input (ventroposteromedial nucleus - VPm) impact sensory processing. We used BiPOLES, specialized optogenetic constructs enabling bidirectional manipulations of neuronal depolarization, to excite and inhibit S1 during a sensory detection task and multisite electrophysiological recordings. In mice trained to report whisker stimuli with a go-no go task, we found that both S1 excitation and inhibition impaired sensory detection. To identify the underlying neuronal mechanisms, we examined how excitation and inhibition altered sensory responses. Although both manipulations reduced sensory responses, they affected neuronal encoding differently: inhibition consistently reduced responses across all layers, while excitation selectively disrupted responses in deep cortical layers (5/6). Because cortical excitability can influence connected thalamic nuclei, we next disentangled intracortical and cortico-thalamo-cortical contributions to S1 excitability by concurrently manipulating S1 and VPm. Preliminary data suggest that excitation, either in S1 and VPm, defines sensory responses, while inhibition impacted sensory responses only in absence of opposing excitatory inputs. We then sought excitability-dependent spiking features mediating behavioral performance. S1 excitation and inhibition increased and decreased stimulus-independent activity, thus making sensory stimuli theoretically less and more detectable, respectively. This contrasted with the inhibition-induced impairment of behavioral detection; thus, we examined neural synchrony. S1 inhibition and excitation reduced stimulus-driven synchrony and enhanced stimulus-independent synchrony, thus consistently reducing stimulus detectability and identifying synchrony as a potential

mediator of sensory detection. Finally, local field potential (LFP) analyses confirmed the excitability-dependent reduction of sensory responses and showed that higher excitability leads to less steep LFP spectral slope, thus linking single-neuron and population activity. Together, our findings suggest that cortical excitability bidirectionally regulates sensory perception by shaping processing in cortex and thalamus, and their interactions, and that these changes in neuronal spiking are reflected at the regional LFP level.

Disclosures: S. Russo: None. **S. Valenzano:** None. **G. Pisicchio:** None. **D. Weiss:** None. **C. Waiblinger:** None. **G.B. Stanley:** None.

Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

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Topic: E.02. Somatosensation – Touch

Support: BSF Grant 2019251
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Title: Left-right redundant vibrotactile detection follows an OR rule yet produces symmetric cortical activity coupled to uninstructed movements

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Abstract: The brain can combine stimuli from both sides to improve object detection. However, the neural mechanisms underlying such bilateral integration are unclear. While some studies have suggested the brain sums inputs across the two hemispheres into a single detector (additive/coactivation model), others have proposed that each hemisphere independently detects its input (OR/race model). Here, we trained head-fixed mice (n = 10) in a redundant vibrotactile detection task in which left whisker, right whisker, or bilateral stimulation instructed a left-port lick (“yes”) following a 500 ms delay, whereas stimulus absence instructed a right-port lick (“no”). Thus, distinct sensory inputs were mapped onto the same delayed report. We fit psychometric functions to the unilateral data and used these fits to generate predictions of bilateral performance under three integration models: OR, additive, and MAX (dominant). The observed performance was best explained by an OR rule, suggesting that left and right vibrotactile inputs are independently detected. Next, we used cortex-wide calcium imaging to investigate the neural correlates of this process. Detected unilateral stimulus trials were accompanied by robust, broadly distributed, and bilaterally symmetric activity throughout the delay period; however, this activity could not be used to decode the stimulus side. This bilateral activation was therefore poorly matched to the lateralized detection suggested by behavior. High-

speed video revealed an explanation: uninstructed body and facial movements ramped immediately after detected stimuli and before the go cue, scaled with stimulus intensity, and developed with learning. Movement-derived pseudo-psychometric and pseudo-chronometric curves mirrored the measured behavioral curves, whereas side decoding from movement remained near chance. These findings suggest that while bilateral detection relies on independent unilateral detectors, the accompanying cortex-wide activity does not represent a side-specific detection signal. Instead, it is primarily driven by rapid-onset uninstructed movements linked to reward expectation. More broadly, redundant perceptual tasks like the one we used provide a useful framework for separating the neural correlates of perception and action by studying how stimulus-specific perception is converted into a stimulus-invariant report.

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Poster

PSTR057: Somatosensation: Thalamic and Cortical Processing

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR057.12/AA24

Topic: E.02. Somatosensation – Touch

Support: NIH R01NS117636

Title: Linking Projection-Defined Corticothalamic Circuits to Behavior in the Mouse Somatosensory System

Authors: *G. R. GILLIE[1], S. R. CRANDALL[2];
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Abstract: Layer 6 corticothalamic (L6 CT) neurons provide the largest input to the sensory thalamus, yet their functional roles remain poorly understood. Work from our lab and others has revealed interesting diversity in CT activity during behavior. In the whisker somatosensory cortex (S1), approximately one-third of CT neurons exhibit whisking-related modulation, with distinct populations showing either increased or decreased firing during active whisking. These findings raise an important question: Do the physiological response properties during behavior relate to distinct subclasses of CT neurons based on their axonal termination patterns in the thalamus? For example, L6 CT neurons in upper L6 of S1 project to the ventral posterior medial nucleus (VPm), the core vibrissal division of the somatosensory thalamus, while those in lower L6 send projections to both VPm and the higher-order posterior medial nucleus (POm). These two subtypes also differ in their intrinsic properties and long-range input from the motor cortex and sensory thalamus, suggesting they may be functionally specialized. Here, we will directly link CT projection identity to in vivo activity patterns in the rodent whisker system. To achieve this goal, we combine juxtacellular recordings with optogenetic targeting and retrograde labeling in awake, head-fixed mice to determine whether projection-defined L6 CT subtypes exhibit

distinct firing patterns during active whisking behavior. This approach enables direct identification of recorded neurons as VPm-only or dual-projecting cells. Understanding how CT diversity maps onto behavioral function will provide fundamental insights into how the cortex regulates thalamic throughput during active sensing.

Disclosures: G.R. Gillie: None. **S.R. Crandall:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.01/AA25

Topic: E.03. The Chemical Senses

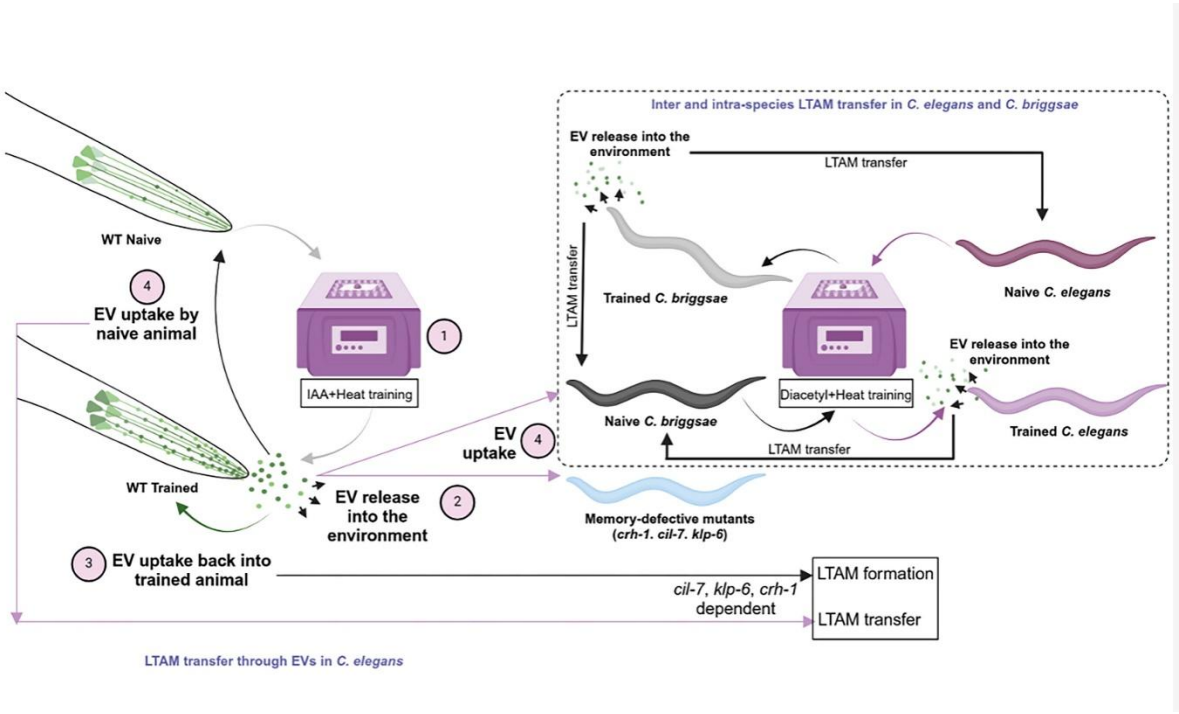
Support: MoE STARS Grant [no. MoE/STARS-1/454]
DBT/Welcome Trust India Alliance Fellowship [grant number IA/S/19/2/504649]

Title: Eavesdropping on worm conversations: investigating the transfer of memory from one worm to another

Authors: *K. BABU;
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Abstract: Native preferences in organisms can be modified through learning. *Caenorhabditis elegans* has proven to be an important model system to study this behavioural plasticity. In this study, we have studied long-term associative memory (LTAM) in *C. elegans* by training worms using two cues- a native chemoattractant and heat as the repulsive cue. This training method results in LTAM formation, observed in the form of loss of attraction to the chemoattractant lasting for upto 24 hours.We show that during training with heat and isoamyl alcohol (IAA), *C. elegans* release factors onto the plate that act as signalling cues for maintaining LTAM. Hence, removal of worms from these plates causes them to lose this memory despite undergoing aversive training. These molecules can in turn be taken up by naïve and memory-defective mutant worms, that have not undergone training, inducing aversive learning in these animals. We further show that the memory is specific to the cue used for training *C. elegans*. In order to investigate the underlying molecular mechanism of this phenomenon, we studied LTAM formation in multiple mutants and found that extracellular vesicles (EVs) sent out by the IL2 neurons in *C. elegans* during training are required for this process. Finally, we show that a single molecule that is released through EVs allows animals to mimic LTAM specifically to IAA when added to the plate.Here, we propose a mechanism by which *C. elegans* upon aversive training, release factors onto the plate through EVs, which can further be taken up by naïve worms (or memory-defective mutants and *C. briggsae*) and induce aversive learning in those animals without any prior training. Our work shows that memory can be transferred from a trained animal to an untrained worm, paving for a new avenue of communication and signaling in *C. elegans*.

A version of this work is available at
https://www.biorxiv.org/content/10.1101/2025.02.26.640282v3



Disclosures: K. Babu: None.

Poster

PSTR058: Olfaction Across Species and Behavior

Location: WCC Halls A-C

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Topic: E.03. The Chemical Senses

Support: NSF Odor2Action (NeuroNex Award #2014217)
NIH Blueprint(D-SPAN) Award (F99/K00- 5K00NS118741-04)

Title: Chemosensory Coding by Tangential Inputs to the Drosophila Navigation Center

Authors: *K. M. NUNEZ[1], K. VAN HASSEL[1], A. LANZ[2], Y. ZAMAN[1], J. FREED[1], A. CARDONA[3], K. NAGEL[4];
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Abstract: Chemosensory cues (odors and tastants) are potent motivators for navigation behaviors, but how chemosensory information is represented within the fly navigation center,

called the Central Complex, is unclear. Here we surveyed chemosensory representations across a large subset of tangential neurons to the fan-shaped body, a region of the Central Complex thought to compute context-dependent goal directions for navigation. Using calcium imaging, validated by whole-cell electrophysiology, we mapped responses to six odors of varying valence and two tastants. We observed robust responses across layers of the fan-shaped body to both attractive and neutral odors, with weaker responses to aversive odors and tastants. Overall response magnitude did not correlate with behavioral valence. While the strongest responses, often within the same neuron, were to apple cider vinegar, a strong attractant, and octanol, a neutral odor, a principal components analysis of tangential neuron representations separated chemosensory stimuli by behavioral meaning. Models based on full brain connectomes predicted some, but not all, of the observed chemosensory responses, and did not segregate stimuli by behavioral meaning. Connectomic pathway analysis suggests that chemosensory responses in tangential neurons derive from many upstream olfactory centers, and identifies downstream fan-shaped body local neurons predicted to respond most strongly to different odors and tastants. Our work illustrates both the power and limits of connectome modeling over many synapses, and will guide future studies of how the fly navigation center orchestrates behavioral responses to chemosensory input.

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Poster

PSTR058: Olfaction Across Species and Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.03/AA27

Topic: E.03. The Chemical Senses

Title: Sustainable Control of Drosophila suzukii using methyl benzoate analogs as repellent agents

Authors: *V. D. SHIELDS[1,2], T. K. HEINBOCKEL[2];
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Abstract: Food security is increasingly threatened by invasive agricultural pests, such as the spotted wing drosophila (SWD), *Drosophila suzukii*. This fruit fly species poses a major risk to global soft fruit production, particularly berries, due to its unique ability to lay eggs in ripening fruits using a serrated ovipositor. Since its initial detection in Hawaii and California, SWD has rapidly expanded its range across the United States, leading to crop losses of up to 80% if unmanaged. This poses significant economic challenges for growers and directly impacts food availability. While synthetic insect repellents like DEET have shown efficacy in reducing infestations, their environmental impact and sustainability concerns have driven the search for greener alternatives. In this study, we investigated the repellency of methyl benzoate, a naturally occurring volatile organic compound, and several of its chemical analogs against SWD.

Repellency assays using 24 female flies per treatment group were conducted across various concentrations and timepoints. Dose-response models were used to calculate RD50 values, enabling a comparative analysis of compound effectiveness. Promising results were observed with anthranilates and ether-substituted benzyl ester compounds, demonstrating a strong potential for the emergence of environmentally friendly repellents. This research contributes to sustainable pest management strategies essential for protecting fruit crops and ensuring long-term food security.

Disclosures: V.D. Shields: None. **T.K. Heinbockel:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

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Topic: E.03. The Chemical Senses

Support: DGAPA-PAPIIT 202724

Title: C58/J mice exhibit altered salience attribution to biologically relevant olfactory cues

Authors: *O. R. HERNANDEZ PEREZ[1], E. ROCHA GONZÁLEZ[2], E. CALLADO[3], E. LUNA CASTAÑÓN[4];
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Abstract: Autism spectrum disorder (ASD) is characterized by social impairments, repetitive behaviors, and atypical responses to sensory stimuli. The C58/J mouse strain displays several ASD-relevant phenotypes, yet its responses to biologically relevant olfactory cues remain poorly understood. Here, we evaluated exploratory behavior and responses to predator-associated stimuli in adult male C58/J mice and C57BL/6J controls using a behavioral battery consisting of the Hole Board (HB), Hole Board with predator odor (HB+Odor), Predator Exposure, and Cotton Swap tests. In the HB test, C58/J mice exhibited reduced latency to initiate exploration, increased locomotor activity, elevated rearing frequency, and increased grooming behavior compared with C57BL/6J mice, indicating enhanced exploratory drive and repetitive behavior. In the HB+Odor paradigm, predator-associated olfactory cues modified exploratory behavior in both strains; however, C58/J mice maintained high levels of exploration and displayed altered investigation patterns toward odor-containing locations. During Predator Exposure, C58/J mice exhibited atypical defensive responses characterized by altered risk-assessment behaviors and reduced behavioral inhibition in the presence of a natural threat stimulus. In the Cotton Swap test, C58/J mice showed altered investigation of relevant olfactory cues suggesting differences in odor processing. Across paradigms, C58/J mice consistently displayed behavioral responses that differed from those of C57BL/6J controls when exposed to ecologically relevant olfactory

stimuli. These findings demonstrate that C58/J mice exhibit a broad alteration in the behavioral processing of biologically relevant sensory cues, encompassing predator-associated stimuli. The combination of enhanced exploration, repetitive behaviors, and atypical responses to olfactory signals suggests altered salience attribution mechanisms that may contribute to ASD-relevant phenotypes. Our results support the use of the C58/J strain as a valuable model for investigating the neural substrates underlying abnormal sensory processing and behavioral responses to emotionally salient environmental information.

Disclosures: O.R. Hernandez Perez: None. **E. Rocha González:** None. **E. Callado:** None. **E. Luna Castañón:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

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Topic: E.03. The Chemical Senses

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NIH UF1NS116241
NIH R01 DC000566
NSF BCS-1926676

Title: Temporal Dynamics of Decision-Predicting Time Cells in Olfactory Discrimination: Molecular and Neural Mechanisms of Associative Learning

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Abstract: In the natural world, animals routinely demonstrate the ability to collect, process, and integrate sensory information about their world to survive, such as finding food, avoiding threats, and selecting mates. Importantly, the effectiveness of these behaviors is rooted in the interplay between olfaction and past experiences, especially influenced by available contextual information. Thus, simply detecting an odor is insufficient; an animal must apply meaning to it and respond appropriately. Previous research has consistently highlighted the hippocampus, particularly the dorsal CA1 (dCA1) region, as a key player in learning and memory processes. In dCA1 there are two molecularly distinct regions of pyramidal cells, deep and superficial, which differ in the expression of Calbindin2. The work presented here utilizes two-photon microscopy and halorhodopsin inhibition to investigate functional differences between these two regions, particularly focusing on temporally distinct divergence in neural activity related to stimulus valence during the associative learning process of the go/no-go task, with a particular emphasis

on the identification of our previously published ‘decision-predicting time cells’. Ultimately, these studies will help to elucidate the roles of Calbindin2 expressing cells during olfactory discrimination, as well as further the field's knowledge on molecular aspects and expression patterns of deep versus superficial dCA1 cells, helping to uncover crucial details about how memories are formed and retrieved in the brain.

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Poster

PSTR058: Olfaction Across Species and Behavior

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National Institute for Theory and Mathematicsin Biology through the NSF (Grant No. DMS-2235451) and the Simons Foundation (Grant No. MPTMPS-00005320)
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Paul G. Allen Family Foundation

Title: Invariance of odor identity encoding in piriform cortex despite variable sniffing behavior

Authors: E. WEI[1], Y. HSU[4], E. BAXTER[2], J. E. FITZGERALD[3], C. E. SCHOONOVER[5], *A. J. P. FINK[1];
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Abstract: Rodents actively sample their olfactory environment, sniffing at rates that can span an order of magnitude. How does the brain extract stable information about odor identity despite moment-to-moment variation in odor sampling? Neuronal activity in the olfactory (piriform) cortex is strongly modulated by the respiratory rhythm, raising the possibility that odor-evoked population activity depends on sniffing behavior. We therefore asked whether piriform odor responses remain stable across natural trial-to-trial variation in sniffing. We simultaneously recorded neuronal activity in the anterior piriform cortex (APC) and sniffing behavior while presenting a panel of chemically distinct odorants. First, we found that sniffing behavior exhibited substantial variability: sniff rate, amplitude, and burst rate varied markedly across trials, including in response to the same odor cue. Second, we found that APC population response vectors also varied across repeated presentations of the same odor. We then asked whether this neural variability could be dissociated from stable, underlying representations of odor identity. Using targeted dimensionality reduction, we identified population activity dimensions associated with sniffing variables and odor identity. This analysis revealed that sniff-related and odor-related dimensions were largely dissociable within APC population activity:

axes that captured variation in sniffing were nearly orthogonal to axes that discriminated odor identity. Consistent with this geometry, trial-to-trial variation in sniffing accounted for little of the variability in the odor-coding subspace. We then performed a regression analysis that removed sniff-related components from neural population activity. Odor identity remained decodable from the sniff-removed representation, providing further evidence that sniff-related and odor-related coding in the APC can be dissociated. These findings demonstrate that piriform activity is modulated by both sniffing behavior and odor identity and that these signals occupy apparently distinct dimensions of neural activity space. This may allow piriform cortex to maintain stable odor encoding despite substantial variability in active odor sampling, permitting reliable olfactory perception during natural behavior.

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Poster

PSTR058: Olfaction Across Species and Behavior

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Topic: E.03. The Chemical Senses

Support: NIH Grant 5R01DC019379-05

Title: Glutamatergic signaling from MCH neurons influences odor memory and metabolism in mice

Authors: *C. WANG[1], A. TROTZ[2], M. KALINOWSKI[2], J. TOLLER[2], L. ALDAY[2], M. HALL[2], K. ALVIÑA[3];
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Abstract: Melanin concentrating hormone (MCH) is an orexigenic hypothalamic neuropeptide that integrates exogenous and endogenous information and regulates several physiological functions including sleep, reproduction, motivated behaviors, feeding and energy homeostasis. The direct projections from hypothalamic MCH-expressing (MCH+) neurons to brain regions such as olfactory bulb, amygdala, piriform cortex, olfactory tubercle and hippocampus, and the distribution of its receptor type 1 (MCHR1), as well as data from MCH knockout (KO) mice have indicated that MCH is also important for regulating olfactory sensory integration and odor memory function. However, the brain circuits involved and downstream mechanisms are still unclear. Considering that MCH+ cells also express glutamate, we hypothesize that glutamatergic signaling pathways from MCH+ neurons influence odor memory and metabolism in mice.To test our hypothesis, we generated mice with reduced glutamatergic inputs from MCH+ cells (crossing MCH-cre with Vglut2floxed mice). We then subjected these MCH-Vglut2floxed mice to a simulated social transmission of food preference (STFP) test, using guanylin exposure to mimic social transmission. Our results showed that losing glutamatergic signaling from MCH+

neurons significantly reduces body weight in a sex and age-dependent manner. Younger Female MCH-Vglut2floxed mice maintained better their body weight under food restriction compared to WT mice, whereas male mice showed no significant difference. During the STFP test, guanylin exposure increased the body weight gain in both young and middle-aged male and female WT mice, with no effects on young and middle-aged female MCH-Vglut2floxed mice. In addition, both male and female MCH-Vglut2floxed mice showed higher preference for demonstrated odor, indicating improvement in odor memory retention without guanylin. These results suggest that glutamatergic inputs from MCH+ cells might be important mediators of the social component of odor memory transmission. We also found that blood ketone levels were elevated in MCH-Vglut2floxed male mice only; whereas lactate levels were increased only in MCH-Vglut2floxed young male and female mice. Our findings indicate that glutamatergic signaling from MCH+ neurons decreases the baseline body weight, slows down energy consumption (female), promote food intake, provides an overall inhibitory effect on socially transmitted odor memory.

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Poster

PSTR058: Olfaction Across Species and Behavior

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Program #/Poster #: PSTR058.08/AA32

Topic: E.03. The Chemical Senses

Title: Olfactory processing impairments induced by stress in juvenile mice

Authors: *L. C. IRVINE[1], J. ZEGERS-DELGADO[1], D. E. MATHENY[1], K. K. N'GOUEMO[1], N. ROSS[1,2], L. B. COOK[1], R. C. ARANEDA[1];
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Abstract: Early life social interactions are essential for normal brain function and behavior, making social isolation a powerful model for studying the impact of early life adversity in the adult nervous system. Accordingly, several studies have indicated that long-term isolation in rodents produces substantial behavioral and neurochemical changes in adulthood. However, little is known about the effects of social isolation during the juvenile period on brain function, especially in the context of sensory processing. Most mammals use olfaction for social behavior; therefore, we investigated the effect of social isolation on olfactory function and behavior in juvenile mice. We show that a 2-week period of social isolation, right after weaning, affects olfactory performance in a sexually dimorphic manner. Isolated male mice, but not females, fail to discriminate between chemically similar odorants in non-social odor discrimination tasks. Using *ex-vivo* electrophysiological recordings we show that isolated male mice show alterations in the main olfactory bulb, including reduced recurrent inhibition and amplitude of inhibitory currents in the output neurons of the bulb, suggesting a shift in the excitation inhibition balance

of these cells. Consistent with these electrophysiological observations, isolated males showed a decrease in newly born granule cells and a reduction in the number of progenitor cells in the subventricular zone. These results highlight the sensitivity of a sensory circuit to social isolation experienced during a vulnerable developmental period.

Disclosures: L.C. Irvine: None. **J. Zegers-Delgado:** None. **D.E. Matheny:** None. **K.K. N'Gouemo:** None. **N. Ross:** None. **L.B. Cook:** None. **R.C. Araneda:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.09/BB1

Topic: E.03. The Chemical Senses

Title: Shaping Odor Perception: Training Olfactory Discrimination in Rats

Authors: *V. D[1], R. WEIR[2], D. RATNAYAKE[3], J. M. SLEZAK[1];
[1]Psychology, Mount St. Mary's Univ., Emmitsburg, MD; [2]Psychology, Mount St. Mary's Univ., Naples, FL; [3]Psychology, Mount St. Mary's Univ., Silver Spring, MD

Abstract: The study of rodents to discriminate and generalize between diverse olfactory stimuli is critical for improving scent detection protocols in applied settings such as the African pouched rats detecting landmines and tuberculosis. In a within-subjects design, male Sprague-Dawley rats (n = 6) were initially trained to press a lever under a Fixed Ratio 1 (FR1) schedule, which was increased to an FR10 schedule for a total of 20 pellets per session. During the discrimination training, rats were presented with either a rosemary essential oil or a non-scent control on a randomized schedule like drug discrimination procedures (e.g., VDVDDDVDVDVV DVDVVVDVDVDD) using a counterbalanced, two-lever choice model. Scents were delivered to each box through tubing connected to a scent diffuser. After every session, the diffuser was cleaned by replacing the essential oil container with a container filled with water and scent-diffuser-tab cleaning solution. The diffuser (with the cleaning solution) was then run until the next session to clear any residual odor. For subsequent sessions, the diffuser was either turned off for non-scent days or refilled with essential oil for scent days. Acquisition of the discrimination was defined as overall responding ≥ 80% on the “correct” lever and = and less than five lever presses (i.e. <50% of the 10 presses required) occur on the incorrect lever before the first pellet delivered during a session. Once criteria were achieved, we tested three carrier oils (fractionated coconut, grapeseed, and apricot oil) to determine an oil that could be used to dilute rosemary oil and did not substitute for rosemary oil. Acquisitions of the rosemary discrimination took approximately 3-4 months of training. Apricot oil was determined to have zero substitution and therefore was used to establish the rosemary oil dose-response curve. Testing of different rosemary concentrations indicated a quantal response as all concentrations tended to have 50% or higher substitution for the training dose. Currently, our study is in progress to further examine the primary chemical constituents common between rosemary and peppermint, isolate and test

compounds unique to rosemary, and determine whether specific molecules cause a distinction and observe behavior, or if the rats are just generalizing to any strong, “cold “essential oil. On average, we have found that peppermint oil shows partial substitution for rosemary. Our results aid the understanding of stimulus in rodent models using olfactory stimuli and translatable significance to applied models of scent detection.

Disclosures: V. D: None. **R. Weir:** None. **D. Ratnayake:** None. **J.M. Slezak:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR058.10/BB2

Topic: E.03. The Chemical Senses

Title: Neural Dynamics Underlying Target-Background Separation in the Olfactory Bulb

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Abstract: Target-background separation is a fundamental yet unresolved problem in sensory neuroscience, particularly in olfaction, where animals must detect behaviorally relevant odor signals within complex, fluctuating mixtures. This project examines how early olfactory circuits implement perceptual segregation at the level of a single, genetically defined glomerular channel (M72S50) and its mitral and tufted cell (MC/TC) output neurons. Using a transgenic mouse line expressing ChR2 in M72S50 olfactory sensory neurons and GCaMP in all MCs/TCs, this project combines optogenetic activation of a single glomerulus with longitudinal two-photon imaging in awake, head-fixed mice performing a go/no-go target-detection task. By systematically varying background odor identity, concentration, and stimulus timing within a sniff cycle, we examine how intra-glomerular interference and inter-glomerular lateral inhibition differentially shape OB output neuron activity and behavioral detectability.Preliminary behavioral data show that mice can be trained to reliably detect target stimulation in the presence of background odors that evoke strong non-target, inter-glomerular activity, independent of target timing within the sniff cycle. Since MCs/TCs are the sole glomerular outputs to cortex, this behavioral robustness contrasts with the suppression of MC/TC activity we observe in passive conditions using identical stimuli. In contrast, background odors that strongly activate the target glomerulus reliably impair detection performance.These findings suggest that lateral inhibition does not impose a rigid constraint on perception, whereas representational overlap at the target glomerulus constitutes a fundamental limit on target-background separation. Accordingly, our central hypothesis is that behavioral state dynamically modulates MC and/or TC activity to maintain target information despite inter-channel lateral inhibition, while overlapping within-channel representations lead to unavoidable perceptual masking

Disclosures: S. Tetrick: None. **M. Karadas:** None. **S.A. Ceballo:** None. **D. Rinberg:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

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Program #/Poster #: PSTR058.11/BB3

Topic: E.03. The Chemical Senses

Support: NIH/NINDS RF1/R01NS128975

Title: Directional sensing of naturalistic odor gradients in olfaction

Authors: *J. SMITH[1,2], I. G. DAVISON[2];
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Abstract: Mice rely heavily on their olfactory senses to navigate complex environments and locate potential food sources. During odor-guided behaviors, animals actively sample non-uniform, spatially varying concentration gradients. Although the way that the main olfactory bulb (MOB) encodes odor identity is well described, much less is known about how it represents spatial information or contributes to the perception of source direction. To mimic the varying spatial relationships and concentration gradients experienced during active search, we developed a spatial olfactometer for positioning point odor sources at varying angles and distances from the animal's nose. Using head-fixed calcium imaging, we show that MOB activity shows robust directional tuning to naturalistic diffusional gradients. Directional information was reflected both in the tuning curves of individual glomeruli, which typically showed peaks biased towards the side of their ‘parent’ hemisphere, as well as in the relative activity levels across the two sides of the MOB, which were most distinct for lateral locations and became similar for cues at the midline. In addition, we used a left-right discrimination task to show that the animals can use these directional sensory signals to accurately judge source direction by licking in the direction of the odor. For sources positioned 10mm from the nose, mice performed with >90% accuracy for the most lateral locations, with accuracy gradually decreasing to chance levels for positions near the midline. The timing of decisions relative to odor onset suggested that animals base their responses on information accumulated over multiple sniffs. Together, our data show robust spatial coding in MOB under naturalistic conditions. Ultimately, combining behavioral discrimination with imaging will help create a foundation for understanding how directional signals inform decision making in olfaction.

Disclosures: J. Smith: None. **I.G. Davison:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

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Topic: E.03. The Chemical Senses

Support: NIH-NCATS CTSA KL2 TR002379
NIH U01-NS128612
NIH R01-MH122258

Title: More Than A Sniff: Interoceptive And Olfactory Integration In The Human Insula

Authors: *P. KEREZOUDIS[1], M. JENSEN[2], B. KLASSEN[3], G. A. WORRELL[1], N. GREGG[3], N. F. INCE[4], J. VAN GOMPEL[4], D. HERMES[5], K. J. MILLER[4];
[2]Neurosci., [3]Neurol., [4]Neurosurg., [5]Physiol. and Biomed. Engin., [1]Mayo Clin., Rochester, MN

Abstract: The insula integrates internal bodily signals with external sensory information, playing a central role in interoception and multisensory processing. While we have previously characterized motor somatotopy and hierarchical speech processing in the human insula, the neural basis of olfactory processing within this structure remains poorly understood. Chemical senses are fundamental to shaping holistic perception of the environment and are thought to coordinate and bind exteroceptive signals. To examine insular contributions to olfactory and respiratory processing, we performed intracranial electrophysiology in patients undergoing epilepsy monitoring and measured high-frequency broadband (HFB) power at rest and during an olfactory paradigm using sniffing sticks with naturalistic odors. We identified distinct regions in the posterior insula exhibiting spectral modulation as a function of respiratory phase, differentially responding to inspiration versus expiration. HFB power increased during odor sniffing relative to both odorless air sniffing and passive inhalation, indicating a stimulus-specific chemosensory response. This neural activity correlated with participants' subjective ratings of odor intensity and unpleasantness, linking local insular activity to perceived salience. These same posterior insular regions were also recruited during speech articulation and orofacial movement, suggesting a role in coordinating respiration with vocalization, swallowing, and oromotor behavior more broadly. Neural responses showed mild habituation with repeated odor presentation, consistent with sensory adaptation. Together, these findings provide new insights into multisensory coordination in the human insula, revealing a posterior insular substrate that integrates chemosensory input with respiratory and oromotor signals and encodes the salience of olfactory experience.

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Poster

PSTR058: Olfaction Across Species and Behavior

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Program #/Poster #: PSTR058.13/BB5

Topic: E.03. The Chemical Senses

Support: NIH BRAIN Initiative U19NS112953

Title: Grounding olfactory perception in language: Benchmarks and models for generating natural language odor descriptions

Authors: *K. TRAN[1,2], K. SAMOILOVA[1], L. STORAN[3], T. LIU[1], A. KOULAKOV[1];
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Abstract: Recent advances in deep learning have enabled prediction of odorant perception from molecular structure, opening new avenues for odor classification. However, most existing models are limited to predicting percepts from fixed vocabularies and fail to capture the full richness of olfactory experience. Progress is further limited by the scarcity of large-scale olfactory datasets and the lack of standardized metrics for evaluating free-form natural-language odor descriptions. To address these challenges, we introduce Odor Description and Inference Evaluation Understudy (ODIEU), a benchmark which includes perceptual descriptions of over 10,000 molecules paired with a model-based metric for evaluating free-form odor text descriptions. The model-based metric uses Sentence-BERT (SBERT) models which are fine-tuned on olfactory descriptions to allow better evaluation of human-generated odor texts. Using the fine-tuned SBERT models, we show that free-form text odor descriptions contain additional perceptual information in their syntactic structure compared to semantic labels. We further introduce CIRANO (Chemical Information Recognition and Annotation Network for Odors), a transformer-based model that generates free-form odor descriptions directly from molecular structure, thus implementing the molecular structure-to-text (S2T) prediction. CIRANO achieves performance comparable to humans. Finally, we generate human-like descriptions from mouse olfactory bulb neural data using an invertible SBERT model, yielding neural-to-text (N2T) predictions highly aligned with human descriptions. Together, CIRANO and ODIEU establish a standardized framework for generating natural language olfactory descriptions and evaluating their alignment with human perception.

Disclosures: K. Tran: None. **K. Samoilova:** None. **L. Storan:** None. **T. Liu:** None. **A. Koulakov:** None.

Poster

PSTR058: Olfaction Across Species and Behavior

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Program #/Poster #: PSTR058.14/BB6

Topic: E.03. The Chemical Senses

Title: Pre-Infection COVID-19 Vaccination Preserves Long-Term Olfactory Function After SARS-CoV-2 Infection

Authors: *S. T. MOEIN[1], R. L. DOTY[2];
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Abstract: Pre-infection COVID-19 vaccination may reduce the risk of persistent olfactory dysfunction following SARS-CoV-2 infection, but objective long-term data remain limited. This confirmatory cross-sectional study tested the hypothesis that vaccination before infection is associated with preserved olfactory function after COVID-19. A total of 424 adults with prior SARS-CoV-2 infection (210 vaccinated before infection, 214 unvaccinated; 292 females, 132 males; mean age=39.0 years) completed validated psychophysical assessments of smell (University of Pennsylvania Smell Identification Test, UPSIT) and taste (Waterless Empirical Taste Test, WETT) an average of more than 1.5 years after infection. Analyses adjusted for age, sex, smoking status, time since infection, and predominant viral variant. Vaccinated participants demonstrated significantly higher UPSIT scores than unvaccinated participants (35.47 vs. 33.50; P=0.002). Unvaccinated individuals were more than twice as likely to exhibit objective olfactory dysfunction (odds ratio=2.44, 95% CI=1.52-3.90). Vaccinated women showed significantly higher UPSIT scores than unvaccinated women (P=0.007), whereas the difference among men did not reach significance. The protective association was most evident among Alpha- and Delta-period infections. In contrast, WETT scores did not differ significantly between groups (P=0.08). These findings provide objective evidence that vaccination before SARS-CoV-2 infection is associated with reduced long-term olfactory dysfunction. The results suggest that vaccination may help preserve olfactory system integrity and mitigate persistent neural consequences of COVID-19 affecting chemosensory function.

Disclosures: S. T. Moein: A. Employment/Salary (full or part-time):; Sensonics International.
R.L. Doty: A. Employment/Salary (full or part-time):; Sensonics International.

Poster

PSTR059: Multisensory Integration Across Model Systems

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR059.01/BB7

Topic: E.08. Multisensory Integration

Support: SNSF Grant P2SKP3_187684
NIH Grant U19NS104653

Title: Locomotory behavior in Hydra vulgaris

Authors: *C. DUPRE[1], J. W. LICHTMAN[2], F. ENGERT[2];
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Abstract: Hydra is a useful animal model to study basic behavior, representing the first instances in evolution to have a nervous system. A freshwater polyp mostly found in ponds and lakes, it is radially symmetric with a body essentially made of a cylinder with a head and tentacles at one extremity and a foot at the other extremity. It can move its body column in various directions in order to explore its surroundings and contract it to hide and escape threats.Using these simple motion primitives Hydra spends most of its time foraging, defined as an exploration of the local environment for food items. The number of components that make foraging behavior is not known, and the temporal structure of this behavior still needs to be elucidated. Hydra is most of the time sessile, i.e. it stays attached with its foot to a substrate. However, it can sometimes move to a different location by somersaulting, which is done by attaching its head to the substrate and detaching its foot in order to reattach it somewhere else. To understand how this feat can be accomplished, we are combining connectomics and behavior analysis to reconstruct the circuitry that generate motion.

Disclosures: C. Dupre: None. **J.W. Lichtman:** None. **F. Engert:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Program #/Poster #: PSTR059.02/BB8

Topic: E.08. Multisensory Integration

Support: Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada.

Title: Aging Influences Cross-Modal Visual Processing in Auditory Cortex

Authors: *Y. MERRIKHI[1], S. G. LOMBER[2];
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Abstract: One of the fundamental roles of the cerebral cortex is to assimilate and synthesize information from various sensory modalities, creating an integrated perception of the environment. While it is well established that auditory areas of cats develop multisensory capabilities within the first six months, the progression of these multisensory functions into adulthood, beyond six months, remains less characterized. This study investigated age-related changes in visually-evoked local field potentials (LFPs) in the primary auditory cortex (A1) and the higher order auditory area, the dorsal zone (DZ). Using laminar arrays of electrodes, we recorded LFP responses in A1 (n=741 recording sites) and DZ (n=525 recording sites) of 6 cats aged 9-36 months under light ketamine anesthesia in response to visual stimulation (80 lux, 500 ms). Our analysis focused on the power and phase consistency of LFP responses, critical indicators previously shown to be affected by cross-modal visual inputs. Our results indicate non-significant and inconsistent correlations between the power of LFP signals and age in DZ

across various frequency bands. In contrast, A1 showed consistently positive, though non-significant, correlations across all frequency bands, with notable strength in the theta (θ; r=0.7, p=0.211) and alpha (α; r=0.726, p=0.102) bands. Significantly, the power of visually-evoked LFP responses in A1 increased relative to DZ with age, particularly in the θ (r=0.822, p=0.045) and α (r=0.902, p=0.012) bands. Similarly, phase consistency of LFP responses in DZ displayed inconsistent, non-significant correlations across frequencies. Conversely, A1 exhibited consistently positive, non-significant correlations, with stronger effects in θ (r=0.635, p=0.175) and α (r=0.643, p=0.169) bands. Notably, as cats aged, the phase consistency of LFP responses in A1 significantly outpaced DZ in the θ (r=0.872, p=0.023) and α (r=0.934, p=0.006) bands. These observations suggest a progressive enhancement in A1's ability to integrate visual stimuli with age, indicative of augmented multisensory processing capabilities in older cats. The increase in LFP response properties (i.e. LFP power and phase consistency) mainly reflects greater synaptic input from visual pathways in A1 as cats age. Our data suggest that this trend does not occur in DZ, highlighting potential regional variations in how the aging auditory cortex adapts to multisensory inputs. This work was supported by grants from the Canadian Institutes of Health Research and the Natural Sciences and Engineering Research Council of Canada.

Disclosures: Y. Merrikhi: None. **S.G. Lomber:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Topic: E.08. Multisensory Integration

Support: JSPS KAKENHI 25H00854
JST CREST JPMJCR22P6
JST CREST JPMJCR25R1

Title: Characterization of Cortical Activity Preceding Sensory-Evoked Pupil Dilation Using Machine Learning

Authors: *M. MORITA[1], T. KOMORI[2];
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Abstract: Cortical activity preceding pupil dilation associated with arousal and cognition is considered the neural substrate of these brain states. Therefore, this study aimed to elucidate the neural basis of somatosensory and visual cognition using pupil dynamics as an index. We hypothesized that sensory stimuli induce pupil dilation via specific cortical activity patterns. To test this, we employed simultaneous measurement of pupil diameter and cortical activity combined with a machine learning approach. Specifically, we constructed machine learning models to predict pupil dilation based on cortical activity associated with hindlimb electrical stimulation, visual pattern stimulation, and visual context stimulation (oddball task). Data

obtained via dual-wavelength wide-field calcium imaging (GCaMP6f) were corrected for hemodynamic artifacts, registered to a standard brain atlas, and subjected to dimensionality reduction using Singular Value Decomposition (SVD). Subsequently, more than 10 independent components were extracted using Independent Component Analysis (ICA). Pupil dilation states were defined based on a specific threshold. Using a Recurrent Neural Network (RNN) on the extracted ICA components and pupil data, we developed a model to predict pupil diameter from cortical activity. The contribution of each cortical region to the prediction was determined using SHapley Additive exPlanations (SHAP). The results indicated that hindlimb electrical stimulation primarily involved the retrosplenial cortex (RSP) and higher visual cortical areas. For visual pattern stimulation, activity in the RSP and anterior visual cortex preceded activity in the dorsal anterior cingulate cortex and motor cortex. Notably, the secondary motor cortex (MOs) was identified as a major component common to both visual pattern and visual context stimuli. In conclusion, we estimated the commonalities and specificities of cortical dynamics during pupil dilation associated with somatosensory and visual cognition, as well as prediction error detection. These findings suggest the existence of a "MOs-LC-Pupil" neural circuit underlying visual cognition.

Disclosures: M. Morita: None. **T. Komori:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Topic: E.08. Multisensory Integration

Support: 1RF1NS127122-01

Title: Behavioral and neural signatures of error detection during virtual-reality navigation in the macaque

Authors: *A. GOJA, Y. GUO, E. FERNANDEZ SANTORO, N. J. MAJAJ, C. SAVIN; New York Univ., New York, NY

Abstract: Successful target-directed navigation requires continuously tracking the discrepancy between planned and actual movement, and revising the trajectory when actions deviate from their expected consequences. How the primate brain identifies such a mismatch, and whether its behavioral consequences are reflected in oculomotor behavior, remains unclear. Two male macaques performed a virtual-reality "firefly" task, steering with a joystick to the remembered location of a briefly cued target (the "firefly") using transient optic flow to indicate the movement. In a subset of trials, we introduced trajectory perturbations in different directions (forward, backward, forward-left, forward-right, backward-left, and backward-right) to induce a controlled mismatch between the planned and actual trajectories. We tracked the animal’s path and eye movements while simultaneously recording from the dorsolateral prefrontal cortex

(dlPFC) and the posterior parietal cortex (area 7a). We compared behavior and neural activity in response to unexpected perturbation to target location and duration matched control trials. We took advantage of past results demonstrating that animals externalize working memory in this task, by keeping track of the location of the invisible target with their gaze, as quantified by a target-tracking index (TTI). Shortly after the onset of perturbations, the animals focused their gaze towards the true target location, suggesting that the animals were aware of the external force being applied and its directionality. The degree of compensation was direction specific, reflecting either differences in detectability of different perturbations or the fact that some perturbations require more substantial corrective actions than others. Population activity in dlPFC and prominently 7a diverged between perturbed and matched control trials, with patterns of directional selectivity similar to those seen behaviorally. Overall, these results indicate that eye movements can provide a behavioral readout of prediction error and compensation, with associated neural correlates.

Disclosures: A. Goja: None. **Y. Guo:** None. **E. Fernandez Santoro:** None. **N.J. Majaj:** None. **C. Savin:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Program #/Poster #: PSTR059.05/BB11

Topic: E.08. Multisensory Integration

Support: IBS-R002-A2

Title: Learning-dependent reorganization of cross-modal inhibitory circuits in the posterior parietal cortex

Authors: I. CHOI[1], ***Y. KIM**[2], S.-H. LEE[3,2,1];
[1]Ctr. for Synaptic Brain Dysfunctions, Inst. for Basic Sci., Daejeon, Korea, Republic of; [2]Dept. of Brain and Cognitive Sci., [3]Biol. Sci., Korea Advanced Inst. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: Opponent inhibition sharpens cortical sensory representations, but whether such an inhibitory regime is innately specified or instead emerges through multisensory experience remains unknown. Here, we measured the effective connectivity between parvalbumin-positive (PV+) inhibitory neurons and neighboring excitatory neurons in the mouse posterior parietal cortex (PPC), a region important for audiovisual integration. Combining two-photon calcium imaging with single-cell-targeted optogenetic stimulation, we found that in naïve mice, auditory-selective PV+ neurons broadly suppressed visual-selective excitatory neurons, constituting a nonspecific auditory-to-visual inhibition. After mice learned an audiovisual Go/No-go congruency task, this inhibition became highly selective: auditory PV+ neurons preferentially suppressed visual excitatory neurons encoding the opposite contingency while sparing those

representing the congruent stimulus, thereby relieving inhibition on congruent visual representations. Thus, PPC neurons in expert mice exert cross-modal opponent inhibition that is absent in naïve animals. Our findings demonstrate that multisensory learning reshapes inhibitory circuits in the association cortex in a contingency-dependent manner.

Disclosures: I. Choi: None. **Y. Kim:** None. **S. Lee:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Program #/Poster #: PSTR059.06/BB12

Topic: E.08. Multisensory Integration

Support: Simons Foundation International SFI-AN-NCSCN-00007276

Title: Neural basis of action planning during echolocation-guided navigation in bats

Authors: *R. KANEKO[1], A. ZHANG[2], X. LAI[2], J. SAYLES[3], D. DRIESKENS[3], N. FINGER[3,4], C. F. MOSS[3,2,5];
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Abstract: Understanding how animals select and plan voluntary actions in dynamic environments remains a fundamental challenge in systems neuroscience. While recent work has illuminated cue-conditioned action selection, how the brain generates self-initiated actions among infinite possibilities in unconstrained, real-world environments is largely unknown. We address this using big brown bats (*Eptesicus fuscus*) as a model. Big brown bats actively control the directional aim and timing of their frequency-modulated sonar calls based on internally stored information and current sensory goals, providing a quantifiable, temporally resolved proxy for spatial attention and prospective action selection unavailable in traditional animal models. We developed a navigational task in which bats must locate a goal from outside a large maze and navigate inside based solely on previously acquired information, without real-time sensory access to the goal. Flight trajectories are captured with high-speed 3D motion tracking, and sonar beam direction, frequency, and intensity are characterized with 360° microphone arrays. Preliminary results indicate that bats plan flight trajectories in advance, utilizing sonar information sampled prior to action initiation. After bats fully learn the task, we conduct wireless multichannel electrophysiological recordings in the hippocampus during free flight. We will discuss hippocampal activity and its potential role in prospective coding in relation to sonar-defined spatial attention and action planning.

Disclosures: R. Kaneko: None. **C.F. Moss:** None.

Poster

PSTR059: Multisensory Integration Across Model Systems

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Program #/Poster #: PSTR059.07/BB13

Topic: E.08. Multisensory Integration

Support: Department of Army Award W911NF-24-2-0004

Title: Testing Cerebellar Contributions to Multisensory Brain-Wide Coordination in Larval Zebrafish

Authors: *M. ALYAMI[1], C. COOMER[2], K. S. JONES[3], D. L. PRITCHETT[1];
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Abstract: The brain must coordinate activity across distributed regions during sensory processing, but whether cerebellar circuits help organize this brain-wide coordination remains unclear. Here, we use larval zebrafish to test how cerebellar activity relates to brain-wide network dynamics during baseline activity, sensory stimulation, and pharmacologically altered brain states. Larvae expressing genetically encoded calcium indicators are imaged with light-sheet microscopy during visual, auditory, and nociceptive stimulation, allowing neural activity to be monitored across multiple anatomically defined brain regions in the intact vertebrate brain. Current work establishes a reproducible experimental and computational workflow for analyzing large-scale light-sheet calcium imaging datasets. This workflow combines preprocessing, motion correction, anatomical registration, activity extraction, region assignment, and network-level analysis to quantify not only which regions respond to sensory input, but also how activity spreads across the brain, how strongly regions couple to one another, and how population activity changes across baseline, stimulation, and recovery periods. Preliminary analyses indicate that propofol anesthesia reduces interregional coupling, supporting the use of brain-state perturbations to identify features of coordinated brain-wide activity.
We hypothesize that multisensory stimulation recruits reproducible coordinated activity states across the larval zebrafish brain and that propofol anesthesia reduces coordination between sensory-responsive brain regions. We further predict that cerebellar activity will be associated with changes in brain-wide coupling during sensory-evoked state transitions. Ongoing analyses will test how sensory-evoked activity patterns differ across baseline, stimulation, and recovery periods, with particular focus on whether cerebellar activity is associated with changes in brain-wide coordination. This project will help define how sensory information is coordinated across the intact vertebrate brain and test whether cerebellar circuits help stabilize distributed neural activity during sensorimotor processing.

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Poster

PSTR059: Multisensory Integration Across Model Systems

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Program #/Poster #: PSTR059.08/BB14

Topic: E.08. Multisensory Integration

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Simons SFI-AN-NC-SCN-00007276-05
ONR N00014-23-1-2086

Title: The midbrain superior colliculus orients eye, pinna and tongue movements in Egyptian fruit bats

Authors: *D. C. DRIESKENS, A. KRISHNA, N. B. KOTHARI, M. JAROSZEWSKI, R. KANEKO, N. M. FINGER, J. SAYLES, C. F. MOSS;
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Abstract: The superior colliculus (SC) is a midbrain sensorimotor hub important for animals to orient in space. Seminal work in traditionally studied species established its role in driving saccades and pinna movements, as well as body and head direction toward goals, and recent work in mice revealed a touch-guided tongue map in SC. Egyptian fruit bats (Rousettus aegyptiacus) offer a unique opportunity to study SC function in a species that combines vision with active sensing via tongue-click echolocation. These bats dynamically steer their sonar beam and independently control eye and pinna positions, providing a rich substrate for investigating the way that the SC coordinates multimodal orienting. We examined the functional organization of the SC in stationary Egyptian fruit bats by electrically stimulating sites across its topography while recording eye, pinna, and ultrasonic tongue-click outputs. Microstimulation evoked tongue-clicks, as well as coordinated eye and ear movements. Eye and pinna responses follow a topographic organization similar to that described in previous studies. Preliminary analyses indicate that evoked tongue-click beams are biased contralateral to the stimulated SC, and we hypothesize that stimulation along the anteroposterior axis systematically modulates the direction of click beams. These results establish the SC as a key controller of this animal's orienting behaviors. Building on these stationary experiments, we aim to extend our study to free-flying bats to determine whether the SC maintains a stable egocentric representation of space with varied weighing of visual and auditory inputs during natural behaviors. Using wireless 64-channel neural loggers and high-speed motion capture, we will record SC population activity while bats navigate complex environments under varying sensory conditions. We hypothesize that while individual receptive fields remain stable, population gain and tuning width will dynamically reconfigure based on the relative reliability of visual and acoustic inputs. Furthermore, we will apply probabilistic population-coding and dimensionality reduction to decode internal goals, predicting that SC neural trajectories will exhibit a rapid bifurcation that signals the animal's transition from exploratory sampling of space to goal-directed landing. Together, these experiments will reveal how the SC integrates multisensory weighting with internal states to guide complex locomotor decisions in an active-sensing animal.

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Poster

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Topic: E.08. Multisensory Integration

Support: Israel Science Foundation
Israeli Council for Higher Education (CHE) via the Weizmann Data Science Research Center
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Title: Global and compartmentalized serotonergic control of sensorimotor integration underlying adaptive behavior

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Abstract: The vertebrate neuromodulatory systems have pivotal roles in controlling adaptive behaviors. Yet, determining their causal effects on neural dynamics has been challenging due to their widespread innervation and the complexity of their receptor signaling. Here, I show that the serotonergic system controls brain-wide neural dynamics through two spatial modes—global and compartmentalized—during motor adaptation in zebrafish. Larval zebrafish adapt their tail motion amplitudes depending on drag force and sensory reafference in a serotonin-dependent manner. Whole-brain neural activity imaging, combined with perturbations of tph2+ raphe serotonin neurons, revealed their spatially distinct effects on behavioral responses: global modulation of locomotor networks and compartmentalized modulation of sensory networks, both synergistically enabling behavioral adaptation. Global modulation occurs through the modulation of a network hub, whereas compartmentalized modulation depends on local serotonin release and receptor expression. Both mechanisms are supported by whole-brain imaging of serotonin release, systematic mapping of serotonin receptors, and integrative computational simulations. Thus, spatially distinct modes of neuromodulation underlie flexible behavior, which can be deciphered through a holistic approach.

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Poster

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Topic: E.08. Multisensory Integration

Support: NIH Grant EY031532

Title: Durability of Visual Restoration After Multisensory Rehabilitation of Hemianopia

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Abstract: Unilateral damage to visual cortex induces a permanent and profound blindness in the contralesional hemisphere of space ("hemianopia"). Our recent work in animals and humans has established that repeated auditory-visual exposure (RAVE) can ameliorate this defect and restore visual responsiveness in physiology, perception, and overt behavior. Recovery with RAVE follows a stereotypic spatial pattern, beginning at the central margin of the sighted field and progressively expanding peripherally. While the functional endpoint after rehabilitation is impressive, the durability and stability of the recovered field has not been established. This study longitudinally tracked the spatial margins and integrity of the rehabilitated visual field in animals (cats, N=3) that were rendered hemianopic by unilateral cortical lesion and rehabilitated with RAVE. Animals were trained to fixate centrally and then detect and localize brief (100 ms) visual stimuli flashed at different eccentricities within the central 120° of space (proficiency was > 80% performance/location). After unilateral lesion of visual cortex, they were unable to detect and localize any visual stimuli presented in the contralesional hemifield. During several weeks of RAVE, they exhibited the characteristic central-to-peripheral pattern of recovery, reaching similar levels of visual detection/localization in the contralesional hemifield as in the ipsilesional (i.e., intact) hemifield (rehabilitated = 87.3%, intact = 92.9%). RAVE was then terminated, and animals were housed normally for several months, with periodic testing but no additional RAVE. After two months, detection/localization performance was marginally but significantly ($p < 0.05$) decreased in the rehabilitated hemifield (rehabilitated = 81.7%, intact = 90.8%). After three months, detection/localization performance significantly declined in both hemifields (rehabilitated = 50%, $p < 0.001$; intact = 80.5%, $p < 0.01$), relative to two months. The spatial pattern of decline in the contralesional hemifield was the reverse of the recovery: at the three-month time point, detection/localization performance at the most peripheral location (-60°) fell to 35.9%, while remaining largely intact (64.1%) centrally (-15°). The performance decrease in both hemifields with time likely reflects an expected general loss of animal task conditioning. The greater loss in the rehabilitated field after three months suggests that the rehabilitative effect is durable but not permanent without additional intervention. This finding suggests that therapies seeking to leverage RAVE should include monitoring and potential re-intervention.

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Poster

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Program #/Poster #: PSTR059.11/BB17

Topic: E.08. Multisensory Integration

Support: TÜBİTAK (Project No: 5240046)

Title: A Novel Radial Flow Assay Reveals Mechanosensory Control of Rheotactic Tracking in Adult Zebrafish

Authors: *N. DÜZ[1], E. ÖZTÜRK[2], S. ANILMAK[2], I. UYANIK[3];
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Abstract: Rheotaxis, the ability to orient and swim against water flow, is a fundamental behavior that enables fish to maintain position and navigate in dynamic aquatic environments. In the absence of visual information, rheotactic behavior relies predominantly on mechanosensory cues detected by the lateral-line system. Quantitative characterization of these sensorimotor responses requires experimental platforms capable of delivering controlled flow stimuli while preserving natural swimming behavior.To address this need, we developed a custom 360° radial flow tunnel that enables freely swimming adult zebrafish to experience precisely controlled changes in flow direction and velocity. The radial flow configuration minimizes directional bias and allows continuous modulation of mechanosensory stimulation without physically restraining the animals. Flow parameters are computer-controlled in real time, enabling systematic investigation of rheotactic tracking performance under dynamic flow conditions.Experiments were conducted under dark conditions to isolate mechanosensory contributions to rheotaxis. A total of ten adult zebrafish were tested while high-speed video recordings captured swimming trajectories and body orientation. Behavioral responses were characterized using both frequency-response and step-response analyses. Gain and phase relationships between imposed flow direction and fish orientation were quantified across different flow conditions.Increasing mechanosensory salience through adjustments in the flow stimulus range improved rheotactic tracking performance. While gain values remained relatively stable, phase lag was substantially reduced, indicating faster behavioral responses and improved synchronization with changing flow directions. Step-response analyses also showed faster responses to flow-direction changes.These results demonstrate that the radial flow tunnel provides a robust and quantitative platform for investigating mechanosensory-guided rheotaxis in freely swimming zebrafish. The system establishes a foundation for future studies examining the neural mechanisms of flow sensing and sensorimotor control in aquatic vertebrates.

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Poster

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Topic: E.08. Multisensory Integration

Support: 1RF1NS127122-01

Title: The temporal structure of reward shapes the explore-exploit balance during macaque virtual-reality foraging

Authors: *Y. GUO[1], E. FERNANDEZ SANTORO[1], V. VENCATO[2], S. FRANCISCO-SIMON[2], J. MORILLO[2], D. E. ANGELAKI[3,1], C. SAVIN[1], N. J. MAJAJ[1];
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Abstract: Adaptive foraging requires balancing exploitation of current resources against exploration of changing alternatives. In this study, we developed a virtual-reality (VR) foraging task for macaques to investigate how this trade-off is shaped by the temporal statistics of reward availability.
Monkeys freely foraged in a virtual arena with three patches (FAST, MED, SLOW), harvesting rewards through button pushes. In each patch, rewards matured progressively with a stochastic delay, signaled by a noisy visual cue; premature attempts failed, resetting the temporal schedule. Different patch types were assigned at random within each block, requiring monkeys to infer box identity based on recent experience. We manipulated the temporal statistics by drawing reward maturation times from two distributions: an exponential distribution with a fixed hazard rate and a gamma schedule, which allows the animal to build expectations about the typical arrival time. Monkey foraging behavior in the VR closely matched that observed in a physical form of the same task, pointing to a common computational strategy across environments. The reward schedule reorganized the monkeys' foraging behavior. Under the exponential schedule, where rewards could become available at any moment, the animal preferred to exploit the richest resource. Normatively, this maximizes reward rate and facilitates inference of patch type at block transitions, especially in regimes with limited sensory information. Under the gamma schedule, where reward was reliably delayed, the monkey could leave FAST immediately after reward collection, to explore lower-quality patches, and later return. The engagement in this behavior differs across subjects and between VR and the physical arena, likely reflecting differences in the cost of moving between patches.
Overall, the patterns of behavior observed in our task demonstrate that animals are sensitive to the temporal structure of reward availability, which they use to navigate the explore-exploit trade-off inherent in foraging. More broadly, we establish a VR platform that can reproduce behavior observed in physical foraging while enabling controlled manipulations.

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Poster

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Topic: E.08. Multisensory Integration

Support: R01 MH-067528
P30 NS-52519

Title: Uni-modal and cross-modal sensory integration in rat brain by fMRI and electrophysiology

Authors: *B. G. SANGANAHALLI, P. HERMAN, J. V. VERHAGEN, F. HYDER; Radiology and Biomed. Imaging, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Sensory integration describes how the brain processes and combines information from different senses. Uni-modal sensory integration (USI) focuses on a single sensory system (e.g., vision or sound), whereas cross-modal sensory integration (CSI) combines different senses (e.g., vision and sound). Understanding USI and CSI enables perception of our environment and has implications on therapeutic recovery of cortical systems after injury. High-field fMRI (11.7T) combined with single-electrode recordings in Sprague-Dawley rats (n = 28; alpha-chloralose) was used to examine USI with bilateral forepaw stimuli generating interhemispheric activations and CSI with forepaw and whisker generating intrahemispheric activations. Somatosensory stimuli included electrical forepaw stimulation (2 mA, 0.3 ms, 3 Hz) and whisker stimulation via air puffs (3 Hz), delivered in a block design. For USI, the left forepaw was continuously stimulated for 90 s while the right forepaw was stimulated for 30 s during ongoing activation, and S1FL activity was examined in both hemispheres. For CSI, continuous forepaw stimulation was paired with unilateral whisker stimulation to probe interactions between S1FL and S1BF cortical representations. Independent stimulation of either forepaw produced robust contralateral S1FL activation consistent with somatotopy. However, sustained bilateral stimulation strongly modulated cortical responses. Ongoing left forepaw stimulation enhanced the BOLD response evoked by right forepaw stimulation, producing an approximately twofold increase in left S1FL responses relative to the contralateral hemisphere, along with elevated prestimulus baseline activity in the opposite hemisphere, indicating interhemispheric state modulation. Cross-modal experiments showed similar effects across somatosensory representations. Concurrent forepaw and whisker stimulation altered both magnitude and temporal dynamics of BOLD responses in S1FL and S1BF. Electrophysiological recordings from both hemispheres confirmed that these hemodynamic effects reflected neuronal modulation. Together, these findings demonstrate that uni-modal and cross-modal sensory integration dynamically modulate cortical activity through interhemispheric and intrahemispheric interactions. Bilateral and concurrent sensory stimulation altered baseline and evoked responses, indicating that sensory representations are shaped by ongoing cortical state. These results improve our understanding of sensory integration in somatosensory networks and may inform mechanisms underlying cortical reorganization and recovery after neurological injury.

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Poster

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Topic: E.08. Multisensory Integration

Support: Israel Science Foundation 1465/20

Title: Dopaminergic neurons drive asymmetric spontaneous activity in symmetrical touch-sensing neurons of Caenorhabditis elegans

Authors: *V. S. BIRARI[1], Y. HAKASPI HUNT[2], I. RABINOWITCH[1];
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Abstract: Bilateral neuron pairs are generally assumed to function symmetrically, yet little is known about whether they also exhibit asymmetric activity. Here we examined the left and right anterior touch receptor neurons (ALM) of *Caenorhabditis elegans*, a pair of anatomically and functionally similar neurons that mediate responses to gentle touch. Using GCaMP6s calcium imaging in microfluidically immobilized animals, we found that spontaneous calcium transients occur in ALM neurons in the absence of external stimulation. In contrast to the synchronized responses evoked by touch, spontaneous activity was largely asynchronous between the left and right ALM neurons and showed no consistent lateral bias. This activity persisted in *mec-4* mutants, indicating that it does not require canonical gentle-touch transduction. Internal state strongly influenced spontaneous ALM activity. Food deprivation increased the frequency of spontaneous transients and frequently produced lateralized activity within the ALM pair. Interestingly, the direction of this asymmetry depended on the side of the animal that contacted the substrate while crawling during food deprivation, indicating that recent sensorimotor experience can shape ongoing activity in these otherwise symmetric neurons. To investigate the circuitry underlying this activity, we acutely silenced dopaminergic neurons using histamine-gated chloride channels. Silencing dopaminergic neurons abolished spontaneous ALM activity, demonstrating that ongoing activity in the touch receptor neurons requires dopaminergic circuit function. These findings reveal a previously unrecognized form of state- and experience-dependent spontaneous activity in the *C. elegans* touch system and show that anatomically symmetric sensory neurons can exhibit independent and dynamically regulated activity patterns.

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Poster

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Topic: E.08. Multisensory Integration

Support: TUBITAK 125E097
TUBITAK 123E155

Title: A deviation from optimal cue combination is not evidence of sub-optimal weighting: the role of active sensing

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Abstract: Optimal cue combination is commonly tested by measuring the reliability of each cue in isolation, inserting those reliabilities into the minimum-variance unbiased estimator, and comparing the predicted combined reliability with behavior. A deviation from this prediction is often interpreted as evidence that animals assign sub-optimal cue weights. This interpretation assumes that the reliability measured in a single-cue condition is the same reliability available during cue integration. Here we show that active sensing breaks this assumption. In active sensory systems, self-generated movements contribute to the same behavioral response from which cue reliability is estimated, and this contribution can increase when sensory information is degraded.

We tested this problem in weakly electric fish performing a refuge-tracking task. Fish were tested with electrosensory information alone or with combined electrosensory and visual information, while water conductivity was changed to manipulate electrosensory reliability without changing the visual cue. Under the standard optimality test, both conductivity conditions should therefore imply the same visual reliability. Instead, the two conditions imply different visual reliabilities, the signature normally interpreted as sub-optimal cue weighting.

We derive an exact variance decomposition showing that the recovered electrosensory variance contains sensory noise, active-sensing variance, and their covariance. Inflation of the electrosensory variance measured in darkness reproduces this discrepancy even when cue integration is optimal, creating an identifiability problem: behavioral second moments alone cannot distinguish genuine sub-optimal weighting from optimal integration measured through an active-sensing-contaminated channel. Finally, an optimal-by-construction integrator passed through the same analysis pipeline reproduces the deviation, showing that the signature does not require weighting sub-optimality. These results show that a deviation from the optimal cue-combination prediction is not, by itself, evidence of sub-optimal weighting. The confound is general to active senses and requires experiments that separate sensory reliability from sensing-related movement.

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Poster

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Topic: E.08. Multisensory Integration

Title: Species-specific effects of water conductivity on refuge tracking behavior in weakly electric fish

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Abstract: Weakly electric fish utilize a specialized active sensory modality, electrosensing, to navigate muddy environments by generating an electric field via their electric organ discharge (EOD). However, active electrolocation is tightly constrained by environmental properties, particularly water conductivity. Acting as the mathematical reciprocal of resistance, high conductivity presents a low load resistance to the electric organ according to Ohm's law. This creates a parallel shunt that causes a drop in external electrical potential, thereby compressing the electric image and degrading sensory contrast. Whether organisms passively tolerate this degradation or activate rapid mechanisms to compensate remains a critical question especially when comparing species with divergent electrogenic architectures, such as the neurogenic *Apteronotus albifrons* and myogenic *Eigenmannia virescens*. In this study, we comprehensively investigated how environmental conductivity shifts shape refuge-tracking behavior in *A. albifrons* and *E. virescens*. Using a fully crossed factorial design, we manipulated illumination, refuge geometry, and water conductivity across diverse sensory conditions. To robustly quantify behavioral metrics, including tracking accuracy (RMSE), consistency (Variability), frequency-domain tracking fidelity (FTE), and mean active sensing power (MASP), we integrated maximum correlation ellipses alongside the variance-calibrated cross-individual bootstrap (CIB-VC) methodology, which significantly enhanced statistical power and resolved subtle kinematic shifts. Our empirical results demonstrate that while high water conductivity impairs temporal precision by reducing tracking gain and increasing phase lag, its ultimate effect is not a uniform suppressive disturbance. Crucially, the interaction between environmental conductivity and illumination revealed distinct statistical variations in tracking performance between the two species. Under varying lighting conditions, the behavioral consequences of environmental short-circuiting manifested differently, demonstrating that sensory cross-modal constraints are deeply intertwined with species-specific sensorimotor and electrogenic capabilities.

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Poster

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Topic: J.03. Anatomical Methods

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Title: Firing Properties of Basal Forebrain Units Across Distinct Projection Populations

Authors: *M. E. LIBERADOR DOS SANTOS NUNES[1], P. VARSANYI[2], P. GOMBKOTO[3], A. VIVEK[4], L. ZABORSZKY[5];
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Abstract: Recent anatomical studies of the rat basal forebrain (BF) cholinergic system have challenged the traditional view of a diffuse ascending modulatory system. By analyzing the spatial relationships between 5,700 cholinergic neurons and their cortical projection targets, three hierarchically organized projection networks were identified: a somatosensory-motor, auditory, and visual (Varsanyi et al., 2025). These findings suggest a modular organization of the BF cholinergic system, but the functional significance of this architecture remains unknown.
To investigate whether anatomical defined BF projection populations exhibit distinct activity patterns during behavior, we recorded extracellular neuronal activity while rats performed a touchscreen visual discrimination task. Spikes were recorded using chronically implanted 64-contact multi-shank probes in the BF, together with 32-contact probes in orbitofrontal cortex (VO/VL) and visual association cortex (V2). BF recording sites were reconstructed within a common anatomical framework, and projection-environment context vectors were computed for each electrode contact across animals (n=4). BF units were isolated using JRCLUST spike sorting followed by manual curation and subsequently registered to reconstructed electrode contacts using probe geometry and shank mapping. This approach linked each recorded unit to anatomical information derived from the BF connectivity dataset.
Preliminary analyses of 155 pooled BF units revealed trends toward differential recruitment of units associated with distinct projection environments during task-related epochs, including pre stimulus, cue, discriminator, and reward periods. Task-related activity patterns in the BF varied among units associated with motor (M1), somatosensory (S1), infralimbic (IL), visual association (V2), and amygdala-related projection populations. These findings provide initial evidence that anatomically defined BF projection populations may exhibit distinct functional dynamics during behavior. Ongoing analyses and additional unit sampling will determine whether specific projection populations preferentially encode behavioral context and transmit specialized information to their cortical targets.

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Poster

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Title: Altered white matter predictors of hMT+ auditory motion responses in early blind individuals

Authors: *L. DAUMAIL[1], K. H. CHANG[2], A. ROKEM[4], I. FINE[3], W. PARK[1];
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Abstract: The human middle temporal complex (hMT+) is classically associated with visual motion processing, but in early blind individuals, the area responds to auditory motion. Auditory motion responses within hMT+ could arise from signals communicated through multiple white matter connections, including thalamocortical pathways, cortico-cortical temporal, or frontal pathways. Here, using combined diffusion and functional MRI datasets, we examined which known anatomical pathways involving hMT+ best predict auditory motion responses in early blind individuals. Eight early blind (3 females, 55.6 ± 15.6 SD years) and 8 sighted controls (4 females, 53.9 ± 13.2 SD years) underwent multi-shell diffusion MRI and standard T2*-weighted functional MRI. Three major white matter pathways associated with hMT+ (thalamic, temporal, and frontal) were reconstructed in each hemisphere using pyAFQ (Kruper et al., 2021, 2025). Endpoint density maps for each tract were computed within a broader lateral occipital region encompassing hMT+ in each hemisphere. Functional motion-selectivity maps were independently obtained by contrasting motion versus stationary audio stimuli in early blind individuals and visual stimuli in sighted individuals. We then used linear regression to examine which endpoint density maps best predicted functional motion-selective responses within hMT+ based on the estimated regression coefficients for each tract. In both groups, endpoint density maps derived from the three tracts significantly predicted motion-selective responses within hMT+. Across groups, the thalamic tract endpoints had the largest regression coefficients in left hMT+, whereas the temporal tract endpoints had the largest regression coefficients in the right hMT+. Importantly, the pattern of tract contributions within the left hemisphere differed between groups. Frontal tract endpoints had larger regression coefficients for auditory motion responses in early blind individuals than for visual motion responses in sighted controls (non-parametric permutation test, $p = .01$). In contrast, thalamic tract endpoints had smaller regression coefficients in early blind individuals relative to sighted controls ($p = .05$). The results suggest that auditory motion responses within hMT+ of early blind individuals may be associated with shifts in underlying structural connectivity patterns, with frontal corticocortical pathways as a potential anatomical substrate.

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Poster

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Title: Neural integration of syntactic structure and visual speech in sentence processing

Authors: *R. PIAO, Y. LI, D. BRANG;
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Abstract: During sentence processing, the brain continuously tracks the speech signal. Prior work suggests that higher-level linguistic information, such as syntax, provides top-down temporal predictions that help organize incoming speech. Conversely, visual speech, the visible articulatory movements, provides bottom-up cues tied to low-level acoustic dynamics. However, how these two sources of information are integrated remains unclear. Here, we test whether syntactic and visual cues contribute independently to neural encoding of audiovisual speech or interact to jointly shape speech encoding. iEEG was recorded from seven epilepsy patients as they listened to 100 English sentences presented in five conditions: a visual-only baseline and four auditory-present conditions varying modality (auditory-alone vs. audiovisual) and degradation (temporally degraded speech, removing primarily envelope fluctuations through amplitude modulation [AM], vs. spectrally degraded speech, perturbing spectral fine-structure via frequency modulation [FM]). At the end of each session, participants were instructed to identify the correct sentence they heard. Analyses focused on the four auditory-present conditions. Behavioral performance is consistent with prior findings, showing that visual speech improves intelligibility of degraded speech and is particularly effective at compensating for disrupted spectral structure during sentence comprehension. For each condition, we fit baseline mTRF models to predict neural responses from acoustic and non-syntactic control predictors. Neural encoding of syntactic structure was quantified as the prediction gain obtained by adding a node-count predictor. The mTRF results showed greater syntax-related enhancement in the audiovisual compared to the auditory-alone conditions, suggesting that visual speech amplifies the contribution of syntactic information to neural encoding. Syntax-related improvements were also larger for FM- than AM-degraded speech, mirroring the behavioral results. Together, these results indicate that syntactic and visual temporal cues interact during continuous speech processing. Both sources of information enable predictions about upcoming speech, suggesting that visual speech strengthens neural tracking of hierarchical linguistic structure through shared, yet complementary, predictive processes.

Disclosures: R. Piao: None. **Y. Li:** None. **D. Brang:** None.

Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.03/BB26

Topic: E.08. Multisensory Integration

Title: Auditory Pitch Biases Predictive Interception Under Visual Uncertainty

Authors: *H. MAHMOUDI, D. A. BARANY;
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Abstract: Interceptive actions require predicting when a moving target will arrive at a critical location. Though interceptive timing is predominantly based on visual motion information, auditory cues have been shown to bias time-to-contact judgments, especially when vision is unavailable or uncertain. Further, consistent mappings between visual and auditory features - such as the association between higher or rising pitches and upward and faster-moving visual targets - can also influence temporal judgments. However, it remains unclear whether auditory influences on predictive interception movements arise from the auditory properties itself or from its correspondence with visual target properties. To address this question, 25 right-handed adults (20 female, 5 male; age 19.8 ± 1.8 years) completed an audiovisual interception movement task in which a vertically moving visual target was briefly occluded prior to the interception zone. Target speed (fast or slow) and auditory cue (rising pitch glide, falling pitch glide, silence) were manipulated across trials. Participants initiated movements earlier during rising pitch trials than during falling pitch and silent trials when measured relative to both target motion onset ($F(2,48)=4.70$, $p=0.014$) and target arrival ($F(2,48)=4.24$, $p=0.020$). Auditory cue presence also reduced temporal estimation bias relative to silence, especially for slower target speeds ($F(2,48)=5.35$, $p=0.008$). In contrast, auditory presence did not significantly affect movement times and endpoint signed error ($p > 0.12$). Interestingly, the rising pitch glide sped up movement initiation and slowed movement times relative to falling pitch glides, independent of congruency with the target speed or direction ($p \leq 0.011$). These findings demonstrate that auditory pitch cues selectively influence predictive timing during interception, with rising pitch cues promoting earlier movement initiation and reducing temporal estimation bias. Moreover, the absence of reliable congruency effects suggests that interception performance is driven more by the auditory cue itself than on its correspondence with visual target properties. Together, these results demonstrate that auditory cues can shape predictive interception performance under visual uncertainty.

Disclosures: H. Mahmoudi: None. **D.A. Barany:** None.

Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.04/BB27

Topic: E.08. Multisensory Integration

Support: NIH NS065395

Title: Sustained neural responses to the visual component of audiovisual speech in human superior temporal cortex

Authors: E. KARN[1], Y. ZHANG[2], J. F. MAGNOTTI[1], X. ZHANG[1], Z. WANG[1], Y. YU[1], K. DAVIS[1], S. A. SHETH[2], H.-C. I. CHEN[1], D. YOSHOR[1], ***M. BEAUCHAMP**[1];
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Abstract: The superior temporal cortex is a key locus for human speech perception. Neural recordings from epilepsy patients implanted with stereotactic EEG (sEEG) electrodes suggest that the superior temporal gyrus (STG) processes auditory (A) speech while the superior temporal sulcus (STS) processes the face and mouth movements visible during visual (V) or audiovisual (AV) speech perception (Zhang et al., *Journal of Neuroscience*, 2025). In that study, only single words were presented, leaving open the possibility that multisensory effects reflected transient responses to word onset. To address this issue, the current study presented stimuli consisting of long narratives (excerpts from stand-up comedy videos). Narratives were divided into 5 second blocks randomly assigned to A, V, or AV conditions and separated by 0.5 second inter-block intervals. The amplitude of z-scored broadband high-frequency activity (BHA, 70-150 Hz) relative to the inter-block baseline was measured in an “early” (transient) analysis window (0 - 0.5 sec after block onset) and a “late” (sustained) analysis window (0.5 - 5 sec). Across 13 participants, 81 STS and STG electrodes were identified as "bimodal" (significant response in the early window to both A and V speech). All electrodes exhibited a sharp initial rise in BHA, peaking approximately 250 ms after block onset. One group of electrodes showed a “visual sustained” response pattern, responding to visual speech in both early and late windows. Another group showed a “visual transient” response pattern, with significant responses to visual speech in the early but not the late window. This was not attributable to overall lower activity, as the early AV response was actually higher in "transient" than sustained electrodes. Response to AV speech were examined; this analysis was unbiased because AV responses were not used for electrode selection or classification. For “sustained” electrodes, there was a significant difference between AV and A responses, with AV > A in both the early and late windows. In contrast, “transient” electrodes did not show a significant difference between AV and A responses in either window (AV ~ A). In the STS, 83% (35 / 42) of electrodes showed a “visual sustained” response pattern, while in STG, 64% (24 / 38) of electrodes showed a “visual sustained” response patterns (p = 0.04 from chi-square). These results support the role of STS in audiovisual speech integration: "visual sustained" electrodes were more common in the STS than the STG, and these electrodes exhibited stronger responses to AV speech than to A or V speech alone, a hallmark of multisensory integration.

Disclosures: E. Karn: None. **Y. Zhang:** None. **J.F. Magnotti:** None. **X. Zhang:** None. **Z. Wang:** None. **Y. Yu:** None. **K. Davis:** None. **S.A. Sheth:** None. **H.I. Chen:** None. **D. Yoshor:** None. **M. Beauchamp:** None.

Poster

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Program #/Poster #: PSTR060.05/BB28

Topic: E.08. Multisensory Integration

Support: Natural Sciences and Engineering Research Council of Canada (NSERC; RGPIN-2020-05927)
Canada Foundation for Innovation (38913 and 41351)
Canadian Institutes of Health Research (PJT 178345 and PJT 185882)
MITACS (IT25405 and Global Link fellowship)

Title: Visual Modulation of Auditory-Cortical Processing during Audiovisual Stimulation in Epilepsy Patients

Authors: *K.-C. LIN[1], J. AHVENINEN[3], H.-Y. YU[4], C.-C. CHOU[4], C.-C. LEE[5], I. P. JAASKELAINEN[6], W.-J. KUO[7], F.-H. LIN[2], H.-J. LEE[2];
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Abstract: Visual cues can shape auditory perception, but the mechanism by which visual information influences the human auditory cortex remains debated. Recent intracranial EEG evidence in epilepsy patients suggests visual stimuli elicited auditory-cortical local field potential and low-frequency oscillatory effects, but did not significantly increase broadband high-frequency activity, a putative correlate of local population firing (Ahveninen et al., 2024). This implies that visual input into the auditory cortex may reflect modulatory changes.
We examined whether visual modulation of the auditory cortex is reflected in fMRI BOLD responses. 13 epilepsy patients underwent presurgical evaluation and participated in the study (6M/7F, range: 15-42 yrs; mean: 26.4 yrs). Second-level GLM analyses were conducted in SPM25 to examine main effects of auditory (tone/white noise), visual(checkboards), and audiovisual stimulation, as well as audiovisual > auditory and auditory > visual contrasts ($p < 0.001$). Significant clusters were anatomically labeled using xjView and reported with cluster size, maximum T values, and MNI coordinates.
Main effects confirmed expected sensory-specific activation patterns. Auditory stimulation elicited bilateral superior temporal and transverse temporal responses(BA41/42/22) while visual stimulation engaged bilateral occipital regions including cuneus, lingual gyrus, middle/inferior occipital gyri, and BA18/BA19. Audiovisual stimulation recruited both auditory temporal and visual occipital cortices. The audiovisual > visual contrast revealed bilateral superior temporal/transverse temporal clusters, (BA41/22), suggesting that the auditory cortex was engaged during audiovisual stimulation relative to visual stimulation alone. However, the

audiovisual > auditory contrast yielded no surviving clusters at the selected whole-brain threshold, indicating that adding visual information to auditory stimulation did not produce a significant additive BOLD increase.
These findings suggest that auditory-cortical activity during audiovisual stimulation is primarily driven by auditory input, while visual information may influence auditory processing in a modulatory manner, potentially through changes in oscillatory state or network-level integration rather than by directly driving additional activation in the auditory cortex. Future analyses may help determine whether audiovisual modulation is organized within a distributed auditory-visual network rather than isolated regional enhancement.

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Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.06/BB29

Topic: E.08. Multisensory Integration

Support: Swedish Research Council Distinguished Professor grant (VR; #2017-03135)

Title: Prediction-error learning drives body ownership updating

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Karolinska Institutet, Stockholm, Sweden

Abstract: Body ownership refers to the perceptual experience that a body part belongs to one's own body. To maintain a coherent sense of bodily self in a noisy and constantly changing sensory environment, and as the body changes throughout life, body ownership must be continuously updated. However, the learning mechanisms underlying body ownership remain poorly understood. The rubber hand illusion (RHI) is a canonical paradigm for studying body ownership, in which participants come to experience a rubber hand as their own after a brief period of synchronous stroking of both the hidden real hand and the visible rubber hand. Previous RHI research has primarily viewed body ownership as a problem of static multisensory integration, clarifying the sensory rules governing ownership reports while largely overlooking the dynamic learning processes through which body ownership is continuously updated. In this study, we developed a RHI paradigm in which participants rated their experience of the illusion on a continuous scale from 0 to 1 following each touch. By manipulating visuotactile asynchrony over time, we aimed to induce different learning curves of body ownership under stepwise or continuous changes in asynchrony. Illusion strength was further manipulated by varying visuo-proprioceptive distance (Near vs Far). To distinguish between competing computational accounts of body ownership updating, we compared a prediction-error (PE) learning model, in which ownership is updated according to the discrepancy between current ownership estimates and

incoming multisensory evidence, and a Bayesian learning model, in which prior expectations are updated across trials through Bayesian inference, against comparison models based on sliding-window averages of recent visuotactile asynchrony and random responding. Model simulations showed that these models predict distinct temporal dynamics of RHI ratings. Behavioral results revealed stable learning curves of the RHI as a function of asynchrony sequences, with higher RHI ratings in the Near compared to the Far condition, indicating that this paradigm captures dynamic changes in body ownership. Model fitting and comparison showed that the PE model outperformed the Bayesian model and both benchmark models, and was the only model able to capture the key characteristics of the RHI rating curves. Cross-validation across blocks further demonstrated superior generalization performance of the PE model. Together, these findings suggest that body ownership is dynamically updated through prediction-error-based learning, with the PE model providing a better account of the observed learning dynamics than Bayesian learning.

Disclosures: S. Xu: None. **H. Ehrsson:** None.

Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.07/BB30

Topic: E.08. Multisensory Integration

Support: NIH NIDCD R01 DC020717

Title: Eccentricity-Dependent Auditory Influences on Visual Cortical Spatial Selectivity

Authors: *T. ZHANG[1], E. CUNNINGHAM[2], W. C. STACEY[3], C. KOHTZ[2], J. HITCHENS[2], D. BRANG[1];
[1]Dept. of Psychology, [3]Neurol., [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Sounds can modulate activity in visual cortex, and attention plays an important role in shaping audiovisual (AV) interactions. However, the neural mechanisms that enable sounds to affect visual processing, and the representational content of auditory responses in visual cortex, remain poorly understood in human. Here, we presented a case study examining how spatially and temporally concurrent sounds affect spatial tuning of visual cortex, using intracranial EEG (iEEG) and population receptive field (pRF) modeling. Auditory and visual stimuli were presented either alone or simultaneously via a custom LED/speaker array spanning ~180° horizontally. One patient completed both a central fixation task (focused attention) - detecting fixation color change in the center of the array - and an audiovisual attention task (distributed attention) - detecting changes in tone frequency or in LED segment color across the full array. This design enabled precise mapping for the spatial tuning of visual, auditory, and AV interaction effects in visual cortex under different levels of spatial attention distribution. We focused on high-gamma power (HGp; 70-150 Hz), a surrogate measure of local spiking activity,

and modeled HGp as a function of stimulus location using a difference-of-Gaussians function. Visually responsive electrodes were identified as those whose pRF models reliably predicted the HGp responses to visual-only stimuli ($R^2 > .5$). Among electrodes surviving this criterion, we observed two classes of visually responsive electrodes: centrally tuned electrodes (with pRF peaks within ±10°) and peripherally tuned electrodes (with pRF peaks beyond ±10°). In centrally tuned electrodes, concurrent sounds reduced visual pRF width without producing consistent changes in pRF peak amplitude or location. In contrast, in peripherally tuned electrodes, sounds shifted pRF peak location without consistent effects on tuning width or amplitude. Moreover, the magnitude of these auditory influences also depended on the interaction between electrode spatial selectivity and the spatial distribution of attention. Together, these findings indicate that visual cortical sites with distinct spatial selectivity profiles integrate sound and visual input differently. These neural differences may underlie eccentricity-dependent behavioral patterns in audiovisual processing.

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Poster

PSTR060: Human Multisensory Integration

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Program #/Poster #: PSTR060.08/BB31

Topic: E.08. Multisensory Integration

Support: NIH Grant R01EY031532
NIH Grant 1T32NS115704

Title: Optimality Versus Individual Variation in Multisensory Integration

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Abstract: Multisensory integration - the neural process of combining information across sensory modalities - is fundamental to perception and behavior. While some reports suggest that neurotypical humans and other animals integrate task-relevant information consistently with information-theoretic principles of optimality, others find substantial individual variation in the multisensory computations of neurotypical humans. To resolve the discrepancy, we studied neurotypical adults in a visual and auditory detection/lateralization task. We hypothesized that subject-level differences in uncontrolled unisensory factors (such as unisensory sensitivity and context-specific unisensory signal filtering) could cause deviation from the characteristic optimal nonlinear computation of neurotypical humans. Subjects underwent a unisensory interleaved staircase calibration procedure without error feedback to assess visual and auditory psychometric sensitivity profiles. Simulations sampling from these profiles demonstrated that even an optimal

multisensory computation yields highly variable apparent multisensory performance if unisensory information levels are not precisely controlled empirically. Subjects were then tested with probability-matched intensity staircases derived from their psychometric sensitivities, without any additional training. After this first testing phase, multisensory performance fell along a continuum from optimal integration to modality-specific dominance. A second calibration phase was then conducted in which subjects were given multiple visual-only or auditory-only staircase trials with error feedback. This training was designed to modify unisensory contextual filtering and did not include any multisensory trials. Subsequent testing revealed that the training shifted the multisensory performance of all subjects towards optimality, with larger effects on subjects whose initial multisensory performance was most deviant. These findings provide a potential resolution to long-standing disputes of optimality vs. individual subject variation in multisensory integration and suggest major sources of individual subject variation observed in the empirical literature are attributable to differences in unisensory function, which can be standardized across subjects by controlling for differences in sensitivity and acuity, and with additional unisensory task training. These subject-level unisensory factors are crucially important in applications seeking to isolate and assess multisensory competencies in neurotypical and clinical populations.

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Poster

PSTR060: Human Multisensory Integration

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Program #/Poster #: PSTR060.09/BB32

Topic: E.08. Multisensory Integration

Support: The Scientific and Technological Research Council of Turkiye, Grant No. 324K405

Title: From Temporal Order to Multisensory Binding:Evidence for Distinct Temporal Processing Deficits in Schizophrenia

Authors: *B. SOYLEMEZ KARAKUS[1,2], S. KOC YILMAZ[3], H. AKTAS DINCER[4], S. BATTAL[5], H. KAFALIGONUL[6];
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Abstract: Schizophrenia has been associated with abnormalities in temporal processing, but it remains unclear whether these reflect a general reduction in temporal precision, a specific

impairment in multisensory temporal binding, or both. Furthermore, it is largely unknown whether multisensory deficits can be explained by impaired unisensory timing. To address these questions, we examined unisensory and multisensory temporal processing within the same cohort. Patients with schizophrenia (SCZ) and healthy controls (HC) completed four tasks: visual and auditory temporal-order judgment (TOJ), audiovisual simultaneity judgment (SJ), and the stream-bounce illusion (SBI). Psychometric functions were fitted for each participant to estimate visual and auditory temporal thresholds and audiovisual temporal binding windows for the SJ and SBI tasks. Group differences were tested using mixed-effects models and Welch t-tests, with permutation tests as confirmation. Hierarchical regression analyses were conducted to determine whether multisensory temporal binding was predicted by unisensory temporal thresholds or by diagnosis. SCZ patients showed reduced unisensory temporal acuity, with elevated thresholds in both the visual (70.8 vs 47.4 ms, d = 0.80) and auditory (87.4 vs 47.9 ms, d = 0.89) TOJ tasks. SCZ patients also exhibited impaired multisensory temporal processing, with broader audiovisual temporal binding windows in the SJ task (655.4 vs 451.3 ms, d = 0.94), and a broader range of audiovisual delays over which sounds altered visual motion perception in the SBI task (d = 0.61). In addition, the point of subjective simultaneity was shifted toward visual-leading audiovisual stimulus pairs, indicating altered calibration of audiovisual timing. Critically, diagnosis significantly predicted audiovisual binding window width ($\Delta R^2 = .16$, $p = .028$), whereas unisensory temporal thresholds did not. These findings demonstrate that schizophrenia is characterized by deficits in both unisensory timing and audiovisual temporal binding. Importantly, multisensory temporal binding abnormalities cannot be fully explained by deficits in unisensory timing, suggesting partially distinct and diverse mechanisms underlying temporal processing dysfunction in schizophrenia (Funding: The Scientific and Technological Research Council of Turkiye, Grant No. 324K405).

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Poster

PSTR060: Human Multisensory Integration

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.10/CC1

Topic: E.08. Multisensory Integration

Support: NSF CAREER 2042251

Title: A generative landmark in the hominoid brain

Authors: E. H. WILLBRAND[1], S. A. MABOUDIAN[1], M. TORRES[2], ***K. S. WEINER**[2]; [1]Univ. of Wisconsin, Madison, WI; [2]Univ. of California, Berkeley, Berkeley, CA

Abstract: Landmarks and biomarkers are critical in neuroscience and medicine across systems and spatial scales. When considering the brain, the shape and features of cortical folds have

genetic underpinnings and continue to change throughout the lifespan. Some of these landmarks serve as diagnostic biomarkers. Nevertheless, certain features of the cerebral cortex have been overlooked, such as tertiary sulci (TS), which are the last indentations to emerge in association cortices. Recent research shows TS predict individual differences in cognitive function with clinical implications in health, disease, and aging. But, several questions remain unanswered. For example, if portions of TS serve as generative landmarks of other anatomical features, such as clusters that are cortically thick or thin, that in turn are different among age groups and clinical populations, as well as are predictive of functional regions and individual differences in cognition.
To begin to fill this gap in knowledge, we focused on a widely studied portion of the hominoid brain: the fusiform gyrus (FG). We tested if there were cortically thick, or cortically thin, locations related to a recently identified landmark, the mid-fusiform sulcus (MFS) across average surfaces. We varied the number of participants (from 10 to 650), age groups (adolescents, young adults, older adults), and clinical populations (Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, and Alzheimer's Disease, as well as Primary Progressive Aphasia and behavioral variants of Frontotemporal Dementia). Across groups, the cortex just anterior to the MFS was uniquely cortically thick (top 5% thickest FG vertices). We subsequently termed this locus the mid-fusiform thickness peak (mFTP). There was higher overlap of the mFTP across averages, age groups, and populations, in the right (mean DICE±SE: 0.69±0.02) compared to the left hemisphere (0.45±0.07; p=.017). We further found that the mFTP was present at the individual level, albeit more variably in size and location from the MFS. Meta-analyses indicate that the mFTP predicts COVID-19 symptoms, schizophrenia polygenic resilience, and is also present in chimpanzees. Finally, the mFTP also putatively co-localizes with one of the fusiform face-selective regions (mFus-faces/FFA-2), more so in the right (DICE=0.24, centroid=6.08mm) compared to the left hemisphere (DICE=0.14, centroid=8.95mm). Taken together, these findings show that the mFTP could serve as a generative landmark in the hominoid brain, which has implications for theories linking brain structure and function to cognition with translational applications and evolutionary insights.

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Poster

PSTR060: Human Multisensory Integration

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Program #/Poster #: PSTR060.11/CC2

Topic: E.08. Multisensory Integration

Support: 1R61MH138705-01

Title: Causal Role of the Right Supramarginal Gyrus in Live Face-to-Face Interaction: Neural and Behavioral Correlates of Eye Movements, Facial Action, and Pupil Dynamics

Authors: *J. HIRSCH[1], N. L. L. RAO[2], J. A. NOAH[3], X. ZHANG[3], S. L. L. SANCHEZ-ALONSO[2], D. PURUSHOTHAMAN[3], V. L. GRACCO[2], M. L. L. TIEDE[3], D. J. OSTRY[4]; [1]Psychiatry, Neuroscience, Comparative Med., Yale Sch. of Med., New Haven, NY; [2]Yale Child Study Ctr., [3]Psychiatry, Yale Sch. of Med., New Haven, CT; [4]McGill Univ., Montreal, QC, Canada

Abstract: Introduction. Although face-to-face interaction between human dyads underlies in-person social behavior, its neural basis remains unknown and represents an emerging focus in social neuroscience. Conventional models of static face processing have prioritized mechanisms in the ventral visual stream[1]. More recent investigations of live interactive faces focus on higher level parietal systems such the right supramarginal gyrus (rSMG[2,3]), but their causal involvement in live interactions has not been established. Here, we test the hypothesis that rSMG is specialized for live face encoding as well as for visual acquisition behaviors (eye movements and pupil dynamics) by transiently disrupting neural activity in the rSMG using focal continuous theta burst transcranial magnetic brain stimulation (cTBS), a form of Transcranial Magnetic Stimulation (TMS). **Methods.** A multimodal hyperscanning system was used to acquire neural signals from functional near infrared spectroscopy (fNIRS) and electroencephalography (EEG), with concurrent eye-tracking, pupillometry, and facial motion before and after cTBS stimulation, during controlled epochs for live face-to-face viewing and face-gaze at a life-like mannequin. In addition to the pre/post TMS neural contrast effects, behavioral measures were regressed on fNIRS signals and compared across conditions to reveal neural correlates of visual acquisition during live face-to-face gaze. **Results.** Neural responses in the rSMG specific to live faces in contrast to the mannequin faces were significantly reduced ($p < 0.05$) following cTBS stimulation, confirming rSMG specificity for live and interactive faces. Further, neural correlates of free-gaze eye-movements, pupil latencies, and facial action units located within adjacent regions were also reduced by the stimulation. **Conclusion.** Findings are consistent with a causal role of rSMG in live and interactive face processing, and contribute to an emerging theoretical framework in which live dyadic interactions exploit multiple highly specialized and coordinated sensory, behavioral, and physiological components. **[1]Kanwisher, N**., J. McDermott and M. M. Chun (1997). "The fusiform face area: A module in human extrastriate cortex specialized for face perception." Neurosci. J **17**(11): 4302-4311. [2] **Hirsch, J**., X. Zhang, J. A. Noah and A. Bhattacharya (2023). "Neural mechanisms for emotional contagion and spontaneous mimicry of live facial expressions."Philos. Trans. R. Soc. B, Biol. Sci.**378**(1875). **[3]Kelley, M**., M. Tiede, X. Zhang, J. A. Noah and J. Hirsch (2025) "Spatiotemporal processing of real faces is modified by visual sensing." Neuroimage **312**: 121219.

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Poster

PSTR060: Human Multisensory Integration

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Topic: E.08. Multisensory Integration

Support: NIH U01 NS117838
NIMH 1R01MH120194
R61 MH135109

Title: Multimodal Recordings Capture Dynamic Event Structure During Real-World Navigation

Authors: *C. S. INMAN[1], T. DAVIS[2], U. TOPALOVIC[5], M. STANGL[7], A. KAZEMI[1], M. HOLLEARN[1], J. CAMPBELL[2], A. TASEVAC[1], L. AUGUSTIN[1], K. OLSON[3], D. ELIASHIV[8], V. R. RAO[10], I. FRIED[11], N. HASULAK[12], S. HILLER[9], L. GARCIA[4], N. A. SUTHANA[6]; [1]Psychology, [2]Univ. of Utah, Salt Lake City, UT; [3]Psychology, Univ. of Utah, Herriman, UT; [4]Kalhert Sch. of Computing, Univ. of Utah, Salt Lake City, UT; [6]Neurosurg. / Biomed. Engin., [5]Duke Univ., Durham, NC; [7]Biomed. Engin., Boston Univ., Boston, MA; [8]Neurol., [9]UCLA, Los Angeles, CA; [10]Neurol., Univ. of California, San Francisco, San Francisco, CA; [11]DEPT NEUROSURGERY, UCLA Sch. Med., Los Angeles, CA; [12]Phoenix Res. Consulting, Phoenix, AZ

Abstract: The ultimate goal of neuroscience is to understand and explain real-world behavior in terms of brain activity and to use these insights to develop therapeutic approaches for neural disorders. Traditional neuroimaging methods, such as fMRI, require participants to remain stationary, which limits the complexity and realism of research studies. By using mobile recording devices synchronized with intracranial EEG recordings in epilepsy patients with an implanted deep brain recording system, we can study the neural basis of everyday human activities such as navigation, wayfinding, and memory encoding in a more natural way that captures the complexity, scale, and functional characteristics of real-world experiences. We asked five RNS participants to learn a 0.75-mile route around campus, providing only instructions to remember the route well enough to navigate back to the starting point. Subjects walked the route 7-8 times over two days, with the 1st walk guided (encoding) and the remaining 6-7 walks navigated by the participant (navigation retrieval). Local field potential (LFP) data between 1-85 Hz were continuously collected throughout each participant's walk, synchronized with a suite of 1st-person experience sensors at millisecond precision (eye-tracking, movement, physiology, video, etc.). We assessed relationships between changes in dynamic event structure, estimated from human event-boundary agreement, and changes in scene representations inferred from computer vision models. This approach revealed a strong temporal correlation between human event boundary agreement and changes in the environmental contents of a scene from a first-person perspective. Other events assessed included subsequent memory effects for landmarks using mobile eye tracking. This analysis revealed that increased foveal visual attention to uncued naturalistic landmarks during real-world navigation predicted later successful memory recognition. Interestingly, this effect was only apparent during the first, second, and last walk relative to the surprise recognition test, reminiscent of well-established primacy and recency effects. Finally, we time-locked hippocampal LFP activity to the first fixation to subsequently remembered and forgotten landmarks and found increases in 4-8 theta activity that were stronger during first learning of remembered landmarks than during later encoding of the same landmarks. This novel, naturalistic cognitive neuroscience paradigm opens new pathways

to studying the neural dynamics of navigation, wayfinding, and memory processes at the temporal and spatial scales of real-world experiences in freely moving humans.

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Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.13/CC4

Topic: E.08. Multisensory Integration

Support: NIH Grant R61MH135405

Title: Context-Aware Multimodal Ecological Research and Assessment Platform Reveals Neural and Physiological Signatures of Anxiety-Memory State During Naturalistic Monitoring

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Abstract: Tracking real-world interactions between internal states (anxiety, memory) and physiological, behavioral, or environmental contexts remains challenging. Current recording systems exhibit technical limitations, confining studies to sparse, limited-modality laboratory measures. To address this technological gap, we developed the Context-Aware Multimodal Ecological Research and Assessment (CAMERA) platform to continuously monitor integrated brain-behavior dynamics in naturalistic settings. CAMERA fuses continuous multimodal streams precisely in real time, including intracranial or scalp electroencephalography (EEG), multi-angle audiovisual recordings, smartwatch physiologic features and smartphone linguistic features. We delivered intermittent tablet-based ecological momentary assessments (EMA) in the epilepsy monitoring unit (EMU), collecting self-reported anxiety ratings alongside performance on a spatial-navigation memory task. CAMERA was deployed in 32 patients (11 stereo EEG, 21 scalp EEG) , with a 124.1 hour mean recording span. In an interim asm-EMA analysis, 496 prompts were delivered; over 80% captured momentary anxiety ratings, and 271 sessions included both the full anxiety assessment and spatial-memory task. EMA-measured anxiety scores strongly correlated with standard clinical anxiety inventories ($p < 0.05$). Linear mixed-effects models

across multiple subjects revealed a significant positive relationship between anxiety state and theta-band power within the hippocampal formation. Furthermore, in the 15-minute windows before each EMA, wristband physiology tracked within-person fluctuations in anxiety and pain across 16 patients: higher anxiety was associated with fewer skin conductance responses, while higher pain was associated with lower skin temperature, greater heart-rate instability, and reduced beat-to-beat heart-rate variability (all $p < 0.05$). Intra-subject analyses further showed correlations between anxiety and fundamental voice frequency ($r = 0.68$) and between anxiety and deep-learning-derived text sentiment ($r = 0.33$). Preliminary findings demonstrate that each modality reliably tracks patient dynamics, suggesting individual associations with measured anxiety and memory state.We validate the CAMERA as a robust platform to map real-world cognitive-affective states with accurate multimodal synchronization, high data completeness, and low latency in naturalistic settings. It offers a generalizable framework for biomarker discovery in systems neuroscience.

Disclosures: H. Zhu: None. **C. Zhao:** None. **C.Z. Han:** None. **L. Wang:** None. **S. Xia:** None. **T. Ehsan:** None. **Y. Li:** None. **L.D. Kolibius:** None. **C.A. Schevon:** None. **R. Auerbach:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH/NIMH, Morgan Stanley Foundation, Erick Shirley Foundation for Mental Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Get Sonar, Inc.. F. Consulting Fees (e.g., advisory boards); The Jake Collective, Get Sonar, Inc., RPA Health Consulting, Inc., Covington & Burling LLP. **J. Ortiz:** None. **A.S. Widge:** None. **B.E. Youngerman:** None. **J. Jacobs:** None.

Poster

PSTR060: Human Multisensory Integration

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Program #/Poster #: PSTR060.14/CC5

Topic: E.08. Multisensory Integration

Support: NIH Grant R01 NS112367

Title: Causal role of cerebellar and multisensory regions in visuo-proprioceptive recalibration of hand position

Authors: J. MATTEN, B. S. ISA, M. WANG, *K. L. FOLCO, H. J. BLOCK;
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Abstract: The weighting and integration of sensory and motor cues is necessary for accurate hand movement, and is constantly updated (recalibrated) to include optimal information that informs action. Recalibration can be experimentally controlled via a mismatch between sensory and/or motor cues. Here we tested the causal effect of three neural regions on sensory

recalibration: the cerebellum (CB), ventral premotor cortex (PMv), or anterior superior parietal lobule (aSPL). We measured visual (V) and proprioceptive (P) variance (reliability) and recalibration before and after reducing activity in the three regions with continuous theta burst stimulation (cTBS). Variance was measured with an upper limb reaching task in a 2D virtual reality apparatus that prevented direct vision of the hands where participants used the right hand to point to the perceived P (the left finger tip), V (a white box), or visual proprioceptive (VP, a white box over the left fingertip) target with no feedback. P-variance was also measured for left hand reaches by having participants reach and then report their finger location on a visually displayed ruler (they could not see their finger). Recalibration was measured in a separate block of the right-hand reaching task where the white box over the left target fingertip was gradually shifted 5 cm from the fingertip. Preliminary data (23-27 subjects per group, about 85% of planned sample) suggested that CB was crucial for recalibration and V reach target estimation, with these participants showing higher V-target reach variance and less recalibration after cTBS than other groups. Both aSPL and PMv cTBS caused an increase in left hand P-variance, but only aSPL cTBS caused greater right hand P-variance. Together, these preliminary results support causal roles of CB, aSPL, and PMv in sensorimotor recalibration. Our results identify a possible multisensory mechanism of recalibration implemented by cerebellar connections with visual and multisensory regions, because visual, not proprioceptive, variance increases were related to cerebellar cTBS.

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Poster

PSTR060: Human Multisensory Integration

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR060.15/CC6

Topic: E.08. Multisensory Integration

Title: Sensory Contributions to Postural Control Differ Across Female Developmental and Reproductive Stages.

Authors: *V. ROBLES-CERDAS, N. SHAH, H. S. BAWEJA;
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Abstract: Female sex hormones fluctuate substantially across puberty, reproductive maturity, the menopausal transition, and post-menopause. These fluctuations may alter sensory integration for postural control, yet their influence remains unclear. Maintaining balance requires the nervous system to weight visual, somatosensory, and vestibular inputs. Hormonal changes over the lifespan may shift how females rely on each sensory channel. Therefore, this study examined sensory integration during postural control across five hormone-status groups in females. We recruited 493 females: pre-pubertal (5-9 years), pubertal (10-14 years), eumenorrheic (15-44 years), peri-menopausal (45-54 years), and post-menopausal (55+ years). Participants completed

the modified Clinical Test of Sensory Interaction in Balance (mCTSIB) on a force plate under four standing conditions: eyes open on firm surface (standard), eyes closed on firm surface (proprioceptive challenge), eyes open on foam (visual challenge), and eyes closed on foam (vestibular challenge). Postural sway increased systematically from standard to vestibular conditions across all sway measures (center of pressure, anterior-posterior, mediolateral; all $p<.001$). Eumenorrheic females swayed less than pre-pubertal, pubertal, and post-menopausal females ($p<.001$). Condition-by-group interactions revealed that post-menopausal females exhibited greater total and mediolateral sway than pubertal and peri-menopausal groups ($p\leq.004$). Anterior-posterior sway was higher in post-menopausal females than all other groups. Under the vestibular condition specifically, post-menopausal females showed the greatest sway in all three sway directions. Overall, these findings indicate that female hormone status is associated with condition-dependent differences in sensory integration during postural control in females.

Disclosures: V. Robles-Cerdas: None. **N. Shah:** None. **H.S. Baweja:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.01/CC7

Topic: F.03. Basal Ganglia

Title: Functional Diversity of Afferent Inputs to the Primary Motor Cortex During Movement

Authors: *S. GEVA[1], J. SCHILLER[2], Y. SCHILLER[3];
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Abstract: The primary motor cortex (M1) serves as a critical integration hub, synthesizing signals from diverse cortical and subcortical regions to generate descending motor commands. Despite its central role, the specific functional contributions of individual input pathways to M1's computational output remain poorly understood. Here, we investigate the encoding strategies of three major M1 afferents: the secondary somatosensory (S2) and secondary motor (M2) cortices, and the ventromedial thalamus (VM). Using in vivo boutonal calcium imaging during motor execution of two different motor tasks we show a fundamental divergence in the information content of these three pathways. While VM thalamocortical inputs exhibit highly uniform firing patterns, information carried by S2 and M2 cortico-cortical inputs are organized into distinct functional sub-groups. Specifically, both S2 and M2 inputs divide into two distinct sub-populations: one that is active during periods of immobility, and others that track the movement across different temporal phases. Generalized Linear Model (GLM) revealed that behavioral variables explained a significantly higher percentage of activity in VM boutons compared to cortical inputs. Tracking identical boutons across both tasks performed on the same day revealed how these pathways adapt to the motor context. We show that VM boutons maintain their high synchrony but shift their firing to align with specific task cues. Meanwhile,

S2 and M2 inputs reliably preserve their distinct sub-population structures, consistently separating into immobility and movement related groups aligned to the task. Finally, we demonstrate that these pathway specific characteristics are disrupted in a Parkinson's disease model. Specifically, thalamic inputs become less synchronous to the task cue, a shift that coincides with motor impairment. These results suggest that a balance of uniform thalamic drive and structured cortical input streams is essential for healthy motor control.

Disclosures: S. Geva: None. **J. Schiller:** None. **Y. Schiller:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

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Topic: F.03. Basal Ganglia

Support: NIH Grant P40 OD010996
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Title: Entering the basal ganglia through a hand muscle

Authors: *C. M. CERKEVICH[1,2], P. L. STRICK[2,1];
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Abstract: The "Body-First" theory of Parkinson's disease (PD) proposes that neural connections provide a pathway for a toxin to spread from the periphery to specific sites within the brain that degenerate as part of the disease process. The potential toxic substances could include environmental toxins (e.g., pesticides, industrial chemicals, and air pollutants), misfolded proteins, or organisms like viruses and bacteria. According to the theory, a toxin would need to travel from the periphery through a chain of at least 6 synaptically connected neurons to reach a key site of PD degeneration— the pars compacta of the substantia nigra (SNpc). It is likely that the toxin would need to replicate (like a prion) and accumulate over a period of years to reach levels sufficient to cause damage in the susceptible neurons.
We tested the biological plausibility of body to brain spread of toxins by using rabies virus as a proxy for a toxin. In essence, we harnessed the unique properties of rabies virus to examine whether the neural connections exist to enable a toxin to travel from a muscle, through a chain of synaptically-connected neurons, to the "right place" in the brain. In this case, the right place is the SNpc.
We chose rabies virus because it allows a rapid and robust test of transneuronal spread. Rabies virus travels exclusively in the retrograde direction, and it has the unique property of moving trans-synaptically from one neuron to another. As an RNA virus, it replicates wherever rough endoplasmic reticulum is present in a neuron. This property results in an online amplification of the toxin.

We injected rabies virus into a single hand muscle, the extensor digitorum communis (EDC) muscle. We selected this muscle because hand symptoms, such as micrographia and a pill-rolling tremor, are often prominent early symptoms of PD. We found that virus traveled through a chain of 6 synaptically-connected neurons to infect SNpc neurons in a time dependent fashion. Throughout the multiple stages of transneuronal transport, infected neurons were limited to the "arm area" in each infected region. For example, the 5th order infected neurons in the putamen and the 6th order neurons in the SNpc were located in the sensorimotor territory at each site. Our results establish the neuroanatomical plausibility of the "Body-first" hypothesis of Parkinson's disease pathogenesis in which a peripheral toxin can exploit multi-synaptic pathways to target specific brain regions central to the disease.

Disclosures: C.M. Cerkevich: None. **P.L. Strick:** None.

Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: NIH F31 NS147428
NIH R01 MH136968

Title: Role of task specific context in multiple motor skill learning

Authors: *S. N. KHIM, A. N. STEIN, S. B. WOLFF;
Pharmacol., Univ. of Maryland, Baltimore, MD

Abstract: A fundamental feature of the brain is its ability to learn and express countless motor skills, yet how related skills influence each other and how the underlying memories are organized within overlapping neural circuits is unclear. Training context may be critical for disambiguating similar skills by providing explicit cues or by allowing skill inference based on task structure. Motor cortex (MC) and dorsolateral striatum (DLS) are network nodes of particular interest for interactions in multi-skill learning, the former due to described representations of context, the latter due to detailed representations of the learned movement patterns of individual skills. Here, we aim to determine how context shapes multi-skill learning on the behavioral level, what role MC plays, and how context affects representations of similar skills in DLS. We take advantage of a rat model of multi-skill learning: rats are trained to press a lever twice with inter-press intervals (IPI) close to a target to gain a reward. Through trial-and-error learning, rats develop idiosyncratic and stereotyped movement patterns, allowing them to reliably produce task-appropriate intervals. Rats are trained on two target intervals sequentially or in parallel, in the same or distinct environmental contexts. Rats trained in parallel learned both target IPIs, but their performance and learning strategies were context dependent. When trained in *distinct contexts (DC)*, rats learned both skills faster, showed greater separation of task-

specific intervals and identified the current task at session onset more quickly than rats trained in the *same context (SC)*. During learning, *DC* rats initially developed intermediate intervals which then diverged towards both targets - potentially reflecting development of distinct skills. In contrast, *SC* rats seemed to learn movement patterns and intervals for the short target and subsequently adapted them for the long target - suggesting adaptation of a shared skill template. Together, this suggests that context biases learning strategies and may affect the relationship between memories during multi-skill learning. We aim to link our findings on the behavioral effects of context on multi-skill learning with the underlying neural circuitry and models of memory formation. Our preliminary findings suggest that the MC→DLS projection, which is dispensable for the execution of individual skills, is important for task-appropriate execution of multiple skills. Our ongoing work explores whether the role of this projection and, using in vivo electrophysiology, the formation and relationship of skill representations in MC and DLS, are affected by context.

Disclosures: S.N. Khim: None. **A.N. Stein:** None. **S.B. Wolff:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.04/CC10

Topic: F.03. Basal Ganglia

Support: F31NS143338

Title: Novel basal ganglia pathways for regulating motor variability

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Abstract: From dancing ballet to tying our shoelaces, complex motor skills are essential for our everyday lives. Over the course of learning these skills there is a notable transition from variable behavior to precise and stereotyped movements. This change in motor variability must be flexible, but also tightly regulated as variability is necessary to explore the motor space to find rewarded solutions, but can also impair peak performance. The mechanisms by which variability is regulated and implemented in the mammalian brain remain unclear. The basal ganglia have been implicated, and a transition from dorsomedial striatum (DMS), associated with variable behavior, to dorsolateral striatum (DLS), driving stereotyped movement patterns, correlates with the decrease in variability during learning. However, how the DMS-DLS transition itself is regulated, remains unclear. Here, we suggest a novel mechanism which contributes to this regulation and thereby to adaptive motor variability during skill learning and execution. The subthalamic nucleus (STN), a node of the indirect pathway, sends largely unexplored feedback

projections to striatum: directly to DLS and indirectly to DMS via the anterior thalamic nuclei (ATN). STN receives broad cortical and subcortical input, allowing an integration of striatal signals with internal and external state information. Based on this, STN is positioned well to modulate the DMS-DLS transition, thereby dynamically regulating motor variability. Indeed, chronic silencing of the STN-DLS projection impairs, while silencing of the STN-ATN or ATN-DMS projections promotes development of kinematic stereotypy and skill learning. Our results suggest novel roles for STN in regulating motor variability, likely by modulating DMS-DLS interplay, and highlight unappreciated complexity in the basal ganglia motor circuitry.

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Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: BRAIN Initiative F32MH125596
BBRF Young Investigator Award
HHMI

Title: Striatal activity maintains a short-term action-outcome memory to guide future choice

Authors: *A. E. GIRASOLE[1], G. MANDELBAUM[2], C. C. BERON[1], M. A. ALBANESE[3], Y. ZHANG[4], B. J. VAN DEN BOOM[1], W. WANG[1], B. L. SABATINI[5];
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Abstract: Adaptive behavior requires animals to use the outcomes of recent actions (action-outcomes) to guide future decisions. While the striatum is critical for decision-making, it is currently unclear how it is involved in the storage and retrieval of short-term associative memories. Here, we implemented a head-fixed memory-guided decision-making task in which mice use the outcome of a previous choice to determine whether to repeat or switch their next action. We show that dopamine fluctuations in the ventrolateral striatum are modulated by reward receipt or omission and recent outcome history, while the activity of direct and indirect pathway striatal projection neurons encodes recent action-outcome associations and predicts future switch/repeat choices. Closed-loop optogenetic activation and inhibition of direct and indirect pathway neurons during either the action-outcome association period or the delay preceding the next choice bidirectionally biased future actions away from those favored by reward history. Together, these findings suggest that striatal activity maintains a short-term action-outcome associative memory that links completed actions to future motor plans during dynamic foraging.

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Poster

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Program #/Poster #: PSTR061.06/CC12

Topic: F.03. Basal Ganglia

Support: T32GM142630
R35NS132213

Title: GPe PV neurons integrate striatal inhibition with subthalamic excitation to regulate naturalistic exploration

Authors: *K. OBERRY, A. H. GITTIS;
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Abstract: The globus pallidus externus (GPe) is a heterogeneous nucleus within the basal ganglia's indirect pathway that has canonically been viewed as a relay involved in motor suppression. However, prior work from our lab found that optogenetic inhibition of parvalbumin-expressing GPe neurons (PV-GPe) in mice failed to produce a cessation of movement but instead elicited avoidance behavior resembling transient punishment. To investigate how GPe dynamics regulate this type of avoidance behavior during naturalistic exploration, we used a multi-novel-object interaction task in which mice could freely explore an arena containing 5 objects (4 novel and 1 familiar). While mice explored, we simultaneously recorded the calcium activity of PV-GPe neurons using fiber photometry. We observed that PV-GPe activity was elevated during object interactions and returned to baseline after the interaction ended. Mixed-effects regression revealed that PV-GPe responses were positively correlated with the duration of object interactions but not by movement velocity, suggesting that PV-GPe neurons encode information about task engagement rather than movement. Optogenetic activation of PV-GPe neurons increased the duration of object engagement, while optogenetic inhibition decreased object engagement duration. Next, to elucidate which inputs shape GPe activity during exploration, we recorded calcium activity of STN or iMSN axons in the GPe using fiber photometry. STN-GPe axon activity showed remarkable similarity to that of PV-GPe neurons, increasing during object interactions, suggesting that the STN activates PV-GPe neurons to support longer object engagement. In contrast, iMSN axons were recruited when animals ceased interacting with an object, suggesting they inhibit PV-GPe neurons to promote object disengagement. Together, our findings indicate that PV-GPe neurons integrate excitatory input from the STN (maintaining engagement) with inhibitory input from iMSNs (promoting object disengagement), thereby shaping distinct aspects of naturalistic exploration.

Disclosures: K. OBerry: None. **A.H. Gittis:** None.

Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

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Title: Striatal dopamine tracks novel arena exploration across multiple timescales

Authors: *M. SVEI[1], A. HARRIS[3,4], H. KWON[5,2];
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Abstract: Dopamine (DA) release in the ventral striatum (VS) is modulated by a variety of motivational factors, including contextual novelty. Previous studies have shown that both discrete novel stimuli and newly available opportunities evoke DA signals much like those associated with reward prediction error signals. Initial encounters with the novel object evoke a prominent DA response, which decrease with repeat exposure if not accompanied by some form of reinforcement. In contrast, the temporal dynamics of DA in novel spatial environments, where novelty is not isolated to a single stimulus object or point location or restricted to discrete moments in time, remain unclear. To address this question, we used fiber photometry and the fluorescent DA sensor dlight1.1 to measure DA release in the nucleus accumbens (NaC) of freely moving mice. On the first recording day, otherwise naïve mice (male and female, 12- 20 weeks) were introduced to one of two distinct open field arenas. After a second session in the environment explored on day one, both groups of mice spent the final recording day in the same arena. Arenas were of the same cross-sectional length but of different shapes (square or 12-sided polygon), and each marked with distinct geometric patterns on three sides. We analyzed fluorescence data along with simultaneously recorded spatial trajectories (extracted from raw video with Deeplabcut) to reveal novelty - associated patterns in DA and behavior at multiple time scales. We found DA responses when mice first approached the arena at the start of each session. These initial event associated peaks were accompanied novel but not familiar environments by a more sustained DA elevation that decayed within minutes. The latter was not explained by height or frequency of transients, seemingly resulting from a seconds-long change to baseline rates of release. Mouse behavior showed similar dynamics. At the start of each session, mice quickly traversed the extent of the arena in a burst of high activity. In familiar contexts, activity quickly dropped to a relatively stable baseline. In novel contexts, activity slowly declined from its initial peak over the course of several minutes. These data provide new

insight into novelty associated DA activity, adding to the findings of several research groups to reveal a role for striatal DA in the real time mediation of spontaneous, self-directed behavior.

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Poster

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Moshinsky fellowship 2019 to F.T.

Title: The substantia nigra pars reticulata encodes outcome more prominently than action during voluntary decision-making

Authors: *J. A. AGUILAR PALOMARES[1,2], J. RAMIREZ-JARQUIN[2], G. B. FLORAN[1], F. TECUAPETLA[2];
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Abstract: The substantia nigra pars reticulata (SNr), a major output nucleus of the basal ganglia, plays a central role in motor control and decision-making. Despite extensive GABAergic projections from SNr neurons to diverse downstream targets, it remains unclear whether these outputs convey overlapping or target-specific information during voluntary behavior. To investigate this, neural activity was recorded in vivo from SNr neurons in freely moving mice performing a two alternative forced choice auditory discrimination task. Recordings were synchronized with high-resolution kinematic tracking (DeepLabCut) to capture behavioral dynamics across distinct task epochs, including stimulus processing, action selection and initiation, and reward evaluation. Task difficulty, movement parameters, and decision-related variables were examined in relation to SNr firing patterns. Population level analyses revealed that SNr activity is functionally heterogeneous. Demixed PCA (dPCA) applied to simultaneously recorded units showed that outcome-related signals dominate population-level variance over motor and sensory variables, suggesting that SNr output encodes the consequences of actions more prominently than the actions themselves. Complementary UMAP clustering identified five distinct functional subpopulations based on temporal activity profiles, further supporting the presence of structured heterogeneity within SNr output. To begin dissecting the anatomical basis of this heterogeneity, an optotagging approach using retrograde viral delivery of ChRmine is being implemented to identify individual SNr neurons based on their projection targets and

examine whether functional subpopulations align with specific downstream pathways. These findings suggest that the SNr does not broadcast a uniform motor command but rather transmits a structured population code that may be organized along target-specific lines. By integrating electrophysiological, kinematic, and anatomical data, this study provides new insight into how basal ganglia outputs support adaptive behavior, with implications for understanding motor and cognitive dysfunction in basal ganglia-related disorders.

Disclosures: J.A. Aguilar Palomares: None. **J. Ramirez-Jarquin:** None. **G.B. Floran:** None. **F. Tecuapetla:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.09/CC15

Topic: F.03. Basal Ganglia

Support: NIH intramural project ZIAMH002956

Title: Small Ensemble Perturbation in Striatum Suggests Strong Recurrent Interactions that Gate Weak Input

Authors: *J. F. O'RAWE, Z. ZHOU, D. STOKES, L. HENRIQUEZ, M. H. HISTED; NIMH, NIH, Bethesda, MD

Abstract: The basal ganglia (BG) has been implicated in gating of information, for example to initiate movements once sufficient input has arrived. However, it is not known how much of this function arises from the macroscopic organization across regions of the BG compared to the local organization within each region. Medium spiny neurons (MSNs) in the striatum send extensive lateral projections to each other. However, MSN-MSN synapses are relatively weak. Here, we directly ask whether the recurrent interactions in the striatum are strong enough to impact network behavior, and whether those interactions can support a gating-like mechanism. We expressed an opsin and calcium indicator in MSNs, and optically accessed the striatum using implanted prisms. Using 2-photon holographic stimulation, we injected excitatory current into small ensembles of ~10 cells and examined the impact in the surrounding network. Using the stimulation response of the targeted cells as a proxy for the strength of input, we find that the striatum is globally suppressed by low input, with the majority of the surrounding network suppressed (pop. mean (% dF/F) = -3.61, 95% CI = [-3.49,-3.73], $t(983) = -60.29$, $p < 0.001$) . However, during high input trials, the striatal network is activated, with the majority of the surrounding network changing its response (pop. mean = 3.38 [3.22,3.53], $t(983) = 42.53$, $p < 0.001$). This remained true after controlling for baseline fluorescence, suggesting this effect is not driven by state-like fluctuations in the network. There was a negative correlation between the low input and high input responses ($r(982) = -0.24$, $p < 0.001$), such that the cells that were more strongly suppressed by the low input were more likely to be the same cells that were more

strongly activated by high input. Comparatively, experiments in V1 using similar protocols show that both low and high input trials increase recurrent responses, but by different amounts (low input pop. mean = 0.53 [0.31, 0.74], $t(2547) = 4.76$, $p < .001$; high pop. mean = 4.19 [3.96, 4.42], $t(2547) = 35.77$, $p < 0.001$). In the cortex the correlation between the low input and high input responses in the network is positive ($r(2546) = 0.68$, $p < .001$), such that cells that were more strongly activated during low input were more likely to be strongly activated during high input. These results provide evidence that the lateral connections between MSNs are in aggregate strong. The local network of the striatum can respond by increasing firing rates even though the MSN local network is entirely inhibitory, likely through disinhibition. Taken together our data show that the local circuits in the striatum may be tuned to gate signals as they pass into the BG.

Disclosures: J.F. O'Rawe: None. **Z. Zhou:** None. **D. Stokes:** None. **L. Henriquez:** None. **M.H. Histed:** None.

Poster

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Topic: F.03. Basal Ganglia

Support: MEXT KAKENHI 23H04976
MEXT KAKENHI 22H05520
JSPS KAKENHI 25K18585
JSPS KAKENHI 20K15942

Title: Basal ganglia output implements value-based decision-making through state destabilization

Authors: *Y. TANIMOTO[1,2], M. TORIGOE[2], T. ISLAM[2], H. KAKINUMA[2], T. SHIRAKI[2], M. LANGE[2], T. ISOMURA[2], H. OKAMOTO[1,2];
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Abstract: To make behavioral decisions, the nervous system undergoes an activity state transition beyond a barrier that lies between the current state and the optimal state. Here, using adult zebrafish, we show that basal ganglia output triggers such state transitions for adaptive behavior. We previously established a virtual-reality system for a Go/No-go task in adult zebrafish and observed the emergence of various task-related neural ensembles in the Dc area of the pallium, the fish homolog of the cortex (Torigoe et al., 2021). In addition, to establish the adult zebrafish brain as a model of the basal ganglia, we generated a comprehensive anatomical map of the zebrafish cortico-basal ganglia circuit, including the cortico-striatal pathways, the direct and indirect pathways, the thalamocortical pathway, and the fish-specific shortcut output pathway from the pallidum to the Dc area (Tanimoto et al., 2024). In this study, we further recorded neural activity from the striatum and pallidum by 2-photon calcium imaging during the

Go/No-go task. After learning the task, their striatal indirect pathway encoded negatively-valued signals preceding failure outcomes, whereas their direct pathway encoded positively-valued signals preceding successful outcomes, both of which are putatively derived from the Dc ensemble activities. Their pallidal output pathway was activated and inhibited by the signals encoded by the indirect and direct pathways, respectively, and then broadcast the integrated signal uniformly across the Dc. Optogenetic activation of this pallidal output pathway destabilized ongoing behavioral states, suggesting that behavioral states transition to a stable point where pallidal output activity is minimized. Mathematical modeling incorporating cortical attractor dynamics showed that simulated pallidal output activity can destabilize ongoing Dc activity states depending on moment-by-moment changes in the output activity, thereby facilitating state transitions toward minimization of the output activity, i.e., the behaviorally optimal state. This mechanism explains why the limited spatial representation in the pallidal output activity can induce the most appropriate behavior from multiple behavioral options.

Disclosures: Y. Tanimoto: None. **M. Torigoe:** None. **T. Islam:** None. **H. Kakinuma:** None. **T. Shiraki:** None. **M. Lange:** None. **T. Isomura:** None. **H. Okamoto:** None.

Poster

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Program #/Poster #: PSTR061.11/CC17

Topic: F.03. Basal Ganglia

Title: Morphology-Driven NMDA Plateau Potentials in Striatal Projection Neurons

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[3]Physiology/Pharmacology, DHSU, Brooklyn, NY

Abstract: Striatal plateau potentials are prolonged, NMDA receptor-dependent depolarizations that provide a concrete electrophysiology readout of synaptic integration in spiny projection neurons (SPNs). We used multicompartment NEURON simulations built from NeuroMorpho.org reconstructions curated from the Luebke datasets to test how three mechanistic axes shape this readout in wild-type (WT) and Huntington's disease (Q175) conditions: (1) morphology, (2) channel conductance, and (3) compartmental context (local dendrite versus soma, both as site of generation and site of measurement). Cohorts included WT (10 D1, 3 D2) and Q175 (15 D1, 27 D2) cells, with identical clustered glutamatergic stimulation (30 synapses, 5 spikes, 3 seeds) to isolate axis-specific effects.Axis 1, morphology: in WT, D1 and D2 morphometrics were not significantly separated, and plateau probability was similar (93.3% vs 88.9%; Fisher p=0.56). Across WT morphologies, shorter dendritic arbors predicted larger somatic plateau amplitude (r=-0.68, p=5e-6), consistent with reduced electrotonic attenuation. In Q175, subtype divergence became strong (length p=0.0002; branch count p=0.0001), and Q175 morphologies produced shorter, less stable plateaus even when

conductances were held at WT values, indicating a morphology-driven electrophysiology deficit.Axis 2, channel conductance: systematic sweeps around fitted baselines identified NMDA and SK conductances as dominant controls of plateau duration, consistent with initiation/sustain versus termination roles. This defines a compact, mechanistically interpretable rescue space for HD-like states.Axis 3, compartments: plateau initiation was dendritic, but circuit-relevant impact depended on somatic expression after cable filtering. Thus, the same local event can produce different output-level signatures depending on dendritic path length and branch architecture.Together, these results support a unifying model: morphology sets transfer gain, channel conductance sets event dynamics, and compartmental context sets observable impact. Plateau potentials therefore bridge structural remodeling and altered electrophysiology in HD, and provide a quantitative framework for subtype-aware, mechanism-guided intervention design.

Disclosures: S. Mitra: None. **S.D. Antic:** None. **W.W. Lytton:** None.

Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: Roy J. Carver Early Career Award (24-5784)
Whitehall Foundation Bioscience Research Grant (2022-05-083))

Title: Striatal Cholinergic Interneurons differentially modulate D1/D2 Medium Spiny Neurons During Movement and Reward

Authors: *B. YUAN[1], J. HE[1], H. GRITTON[2];
[1]Univ. of Illinois Urbana-Champaign, Champaign, IL; [2]Comparative Biosci., Univ. of Illinois, Urbana, IL

Abstract: The striatum is the primary input nucleus of the basal ganglia, integrating cortical and thalamic signals to shape motor output. Canonical models propose two functionally opposing pathways: D1 dopamine receptor-expressing medium spiny neurons (D1-MSNs) facilitate movement through the direct pathway, whereas D2 dopamine receptor-expressing medium spiny neurons (D2-MSNs) suppress movement through the indirect pathway. However, growing evidence suggests that these populations operate in a coordinated manner during voluntary behavior. We previously demonstrated that striatal cholinergic interneurons (CHIs) coordinate MSN network activity during locomotion, with CHIs synchronizing MSN ensembles and signaling movement-bout termination. Building on these findings, we sought to determine how CHIs influence interactions between genetically identified D1- and D2-MSN populations during motor behavior and reward-related events. To address this question, we performed simultaneous in vivo calcium imaging of genetically identified CHIs, D1-MSNs, and D2-MSNs in the dorsolateral striatum of freely moving mice. Cell-type-specific activity was recorded during

spontaneous locomotion and reward-related behaviors on a virtual treadmill, allowing us to quantify relationships between CHI activity, cell specific MSN population activity, and behavioral state transitions. Consistent with previous reports, all three populations exhibited robust movement-related activity. D1- and D2-MSN ensembles more faithfully encoded the duration and structure of movement bouts than CHIs. Preliminary within-cell-type analyses reveal that CHI spike timing is associated with differential changes in D1- and D2-MSN population synchrony during behavioral states transitions including movement initiation and reward-related events. These findings also suggest that CHI activity may be permissive for motor-plan transition initiation as well as movement termination.

Disclosures: B. Yuan: None. **J. He:** None. **H. Gritton:** None.

Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: NIA Intramural Research Grant ZIAAG000928

Title: Involvement of endocannabinoid signaling in midbrain dopaminergic neurons during interval timing

Authors: *L. WANG[1], D. BASU[1], V. MARTINEZ SMITH[3], H. CAI[2];
[2]Neurogenetics, [1]Natl. Inst. on Aging, Bethesda, MD; [3]NIA/NIH, Bethesda, MD

Abstract: Interval timing—the conscious perception of time on the scale of seconds to minutes—is critical for daily functioning. Deficits in interval timing have been implicated in several neurological disorders, including Parkinson's disease (PD), in which patients tend to overproduce single time intervals and exhibit a migration effect when estimating multiple intervals. Interval timing depends on corticostriatal circuits, with dopamine playing a key role. However, how dopaminergic signaling is modulated during interval timing remains unclear. We hypothesized that endocannabinoids (eCBs), particularly *2-Arachidonoylglycerol* (2-AG) produced by midbrain dopaminergic neurons, play an important modulatory role in interval timing. To test this, we generated transgenic mice with a conditional deletion of ***Dagla*** and ***Daglb***, the primary enzymes responsible for synthesizing 2-AG in midbrain dopaminergic neurons (DANs). These mice were tested using nose-poke-based interval timing tasks. In a task with a single 30-second criterion interval, mice lacking both ***Dagla*** and ***Daglb*** in DANs significantly overproduced the interval, whereas mice lacking only ***Dagla*** or ***Daglb*** did not. In a dual-interval task (15s and 30s), mice lacking either ***Dagla***, ***Daglb***, or both in DANs exhibited a migration effect—overproduction of the shorter interval and underproduction of the longer one. Fiber photometry recordings in control mice showed a ramping increase in dopamine release in the dorsomedial striatum (DMS), but not in the dorsolateral striatum, leading up to the criterion

interval. This ramping dopamine release in the DMS was absent in the transgenic mice deficient in 2-AG production in DANs. To further investigate the input pathways through which 2-AG may influence DANs, we selectively blocked GABAergic or glutamatergic transmission onto a subset of DANs during the task. Interestingly, though blocking both types of transmission impaired task performance, blocking glutamatergic transmission resulted more profound deficits, including migration effect on both interval accuracy and precision. Together, our results reveal a novel modulatory role for eCBs produced by midbrain DANs in time perception and provide circuit-level insight into the timing deficits observed in Parkinson's Disease.

Disclosures: L. Wang: None. **D. Basu:** None. **V. Martinez Smith:** None. **H. Cai:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR061.14/CC20

Topic: F.03. Basal Ganglia

Title: Antipsychotics with different mechanisms of action display distinct neural activation profiles in the striatum

Authors: *E. A. PETTER[1], O. H. MILLER[2], L. A. TAN[3], L. BELLIER[4], M. E. MODI[1], D. CHENG[5], S. HUANG[4], Z. BALEWSKI[6], J. J. NASSI[7], R. J. KLEIMAN[8], J. M. BROOKS[1]; [1]Res., Alkermes, Waltham, MA; [2]Johnson & Johnson Innovative Med., Del Mar, CA, ; [3]Biol., Alkermes, Inc, Waltham, MA; [4]Inscopix Discovery Lab; Inscopix, a Bruker Company; Mountain View, CA, Mountain View, CA, ; [5]Inscopix, A Bruker Co., Mountain View, CA, ; [6]Univ. of California, Berkeley, Berkeley, CA, ; [7]Inscopix Discovery Lab., Inscopix, a Bruker company, Poway, CA; [8]Res., Myrobalan Therapeut., Sharon, MA

Abstract: Psychosis is associated with a hyperdopaminergic state in the striatum, a feature that can be modeled preclinically with amphetamine administration. Although amphetamine-induced hyperlocomotion is commonly used as a behavioral proxy for this state, it has limited utility for differentiating between compounds. Prior evidence suggests that circuit-level readouts may provide greater resolution. Increased dopamine is thought to differentially modulate striatal direct and indirect pathways, which are composed of medium spiny neurons (MSNs) expressing D1 or D2 receptors, respectively. Therefore, direct measurements of D1- and D2-MSN activity may provide a more discriminating framework for characterizing antipsychotic mechanisms of action. Using miniscope-based calcium imaging, we measured the neural activity of D1- (N=9) or D2-MSNs (N=13) in the dorsomedial striatum of mice as they freely explored an open field. Neural activity was analyzed separately during periods of rest and movement. During calcium imaging, animals were injected with amphetamine to recapitulate the hyperdopaminergic state associated with psychosis. We then administered one of four compounds that have been tested as antipsychotics (clozapine, MP-10, ecopipam, or haloperidol) to assess their neurobehavioral profiles. All compounds normalized amphetamine-induced hyperlocomotion, confirming that

behavioral measures alone were insufficient to differentiate between them despite their varied pharmacologies. In contrast, each compound had distinct effects on D1 and D2 MSNs following amphetamine administration. Hierarchical clustering of multidimensional neurobehavioral metrics successfully segregated compounds according to their mechanisms of action, despite the analysis being agnostic to pharmacology. These findings demonstrate that combining circuit-level measurements with behavioral assays enhances compound differentiation in an amphetamine-induced hyperlocomotion model.

Disclosures: E.A. Petter: A. Employment/Salary (full or part-time):; Alkermes. **L.A. Tan:** A. Employment/Salary (full or part-time):; Alkermes. **M.E. Modi:** A. Employment/Salary (full or part-time):; Alkermes. **J.J. Nassi:** None. **R.J. Kleiman:** A. Employment/Salary (full or part-time):; Myrobalan Therapeutics. **J.M. Brooks:** A. Employment/Salary (full or part-time):; Alkermes.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.15/CC21

Topic: F.03. Basal Ganglia

Title: Whole-Brain Input Organization of Kremen1-Positive Striatal Spiny Projection Neurons Revealed by Monosynaptic Rabies Tracing

Authors: *V. M. MARTINEZ SMITH;
LNG, NIA/NIH, Bethesda, MD

Abstract: Whole-Brain Input Organization of *Kremen1*-Positive Striatal Spiny Projection Neurons Revealed by Monosynaptic Rabies TracingVictor M. Martinez Smith, Jie Dong, Ronald Paletzki, Lisa Chang, Lupeng Wang, Charles R. Gerfen, and Huaibin Cai
The dorsal striatum integrates cortical, thalamic, and neuromodulatory signals to regulate motor control and decision making. Understanding how distinct subtypes of striatal spiny projection neurons (SPNs) receive and process these inputs is critical for elucidating basal ganglia function. *Kremen1*-positive (*Kremen1*$^{+}$) SPNs represent a molecularly defined SPN subtype that is enriched within patch (striosome) compartments of the dorsal striatum, yet their afferent connectivity remains poorly understood. To characterize the circuits that provide input to these neurons, we employed monosynaptic rabies virus tracing in *Kremen1*$^{2A\text{-}Cre}$ knock-in mice. Starter cells were broadly distributed along the rostrocaudal axis of the dorsal striatum. Whole-brain mapping demonstrated that *Kremen1*$^{+}$ SPNs receive substantial inputs from motor, somatosensory, and prefrontal cortical regions, as well as from multiple thalamic nuclei. Additional afferent projections originated from the amygdala, basal ganglia, and midbrain structures, including dopaminergic populations. Quantitative analyses further revealed a strong predominance of sensorimotor-related inputs compared to other brain regions. Together, these findings indicate that *Kremen1*$^{+}$ SPNs are positioned to integrate diverse cortical, thalamic, and

neuromodulatory signals, with a particular emphasis on sensorimotor information. This comprehensive whole-brain input map provides new insight into the connectivity of a patch-enriched SPN subtype and establishes a foundation for investigating how *Kremen1*$^{+}$ SPNs contribute to basal ganglia circuits underlying motor function and behavior.

Disclosures: V.M. Martinez Smith: None.

Poster

PSTR061: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: Tourette Association of America
New Jersey Center for Tourette Syndrome
NINDS

Title: Investigating dopamine-dependent motivational salience attribution in Tourette syndrome

Authors: *D. G. YILMAZ, T. KOWALSKI, R. WANG, M. TISCHFIELD;
Cell Biol. and Neurosci., Rutgers Univ., Piscataway, NJ

Abstract: Tourette syndrome (TS) is hypothesized to involve changes in sensorimotor processing, associative learning, action selection, and dopaminergic signaling. These changes are postulated to underlie tics: compulsive, habit-like behaviors performed to relieve unpleasant somatosensory phenomena (urges). We hypothesized that premonitory urges may manifest from aberrant salience attribution to sensory cues, leading to heightened stimulus-driven behaviors that develop in a dopamine-dependent manner. Utilizing mice expressing a mutation in a high-confidence risk gene, Celsr3-C1906Y, we modeled tic formation as a sensorimotor learning process arising from aberrant salience assignment to non-instrumental stimuli, while recording dopamine dynamics in the nucleus accumbens (NAc), a key region for assigning motivational salience. First, we tested if TS mice exhibit increased cue-oriented behavior in an appetitive classical conditioning paradigm using a retractable lever as conditioned stimulus (CS). We saw no genotype differences in cue-approach behavior, and accompanying NAc dopamine dynamics upon CS presentation, approach, and reward consumption were also similar. Second, we tested whether previously learned associations in TS mice trigger a surge in expression of learned actions using a Pavlovian-to-instrumental transfer (PIT)-like paradigm. Although TS mice displayed significantly faster instrumental responding, this increase was not contingent on CS presentation, suggesting a generalized acceleration of motor responding, rather than cue-evoked invigoration. Our results suggest tics may manifest from changes to action selection parameters (e.g. bias for acting), potentially involving dorsal striatal circuits, rather than changes to motivational states induced by heightened cue saliency and altered NAc dopamine.

Disclosures: D.G. Yilmaz: None. **T. Kowalski:** None. **R. Wang:** None. **M. Tischfield:** None.

Poster

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Topic: F.03. Basal Ganglia

Support: 1F31NS135969

Title: Changes to striatal dopamine in Celsr3 TS mice underly compulsive-like and hard to suppress behaviors

Authors: *T. F. KOWALSKI;
Neurosci., Rutgers Univ. - Keck Ctr. for Collaborative Neurosci., Piscataway, NJ

Abstract: Tourette syndrome (TS) is a neurodevelopmental disorder associated with alterations in cortico-striatal circuits and dopamine signaling that result in tics - stereotyped, repetitive movements or vocalizations often preceded by premonitory urges. Human studies have demonstrated increased reliance on habitual behavior and stronger perception-action associations in individuals with TS, suggesting that the disorder involves cognitive alterations in action learning and control. Therefore, we hypothesize that tic learning and reinforcement arise from disrupted motor learning and control processes. To investigate this, our lab is utilizing a novel genetic mouse model harboring a mutation in the high-confidence TS risk gene, *Celsr3*. Using this model, we are examining changes in reinforcement learning and cognitive control while recording *in vivo* striatal dopamine dynamics. Our previous work has demonstrated that *Celsr3* TS mice exhibit compulsive grooming, as well as repetitive rearing, which is attenuated by dopamine-targeting drugs. Building upon these findings, we now show that *Celsr3* TS mice, during reinforcement learning assays, acquire motor associations more rapidly, resulting in heightened motor responding and deficits in behavioral suppression. These phenotypes are accompanied by temporally and spatially distinct alterations in dorsal striatal phasic dopamine signaling, suggesting a potential mechanism underlying exaggerated early motor learning in *Celsr3* TS mice. Furthermore, when tested under the dopamine D1 receptor antagonist ecopipam, *Celsr3* TS mice exhibit differences in the degree of behavioral rescue depending on when treatment is initiated during reinforcement learning, suggesting that early learning stages may be critical for the development of more compulsive-like and hard to suppress behaviors in these mice. Together, these findings provide a novel framework for understanding how dopamine dysregulation may contribute to behavioral manifestations of TS and may inform the development of future targeted interventions for this disorder.

Disclosures: T.F. Kowalski: None.

Poster

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Program #/Poster #: PSTR061.18/CC24

Topic: F.03. Basal Ganglia

Support: R21-EY029091
R01-EY022411
P30 EY001583

Title: Neural correlates of deliberative decision-making in the monkey zona incerta

Authors: *L. DING[1], K. BRANAM[3], J. I. GOLD[2];
[1]Dept. of Neurosci., [2]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [3]Neurosci., Univ. of Arizona, Tucson, AZ

Abstract: Deliberative saccade decisions are formed in the oculomotor system via an embodied process involving cortical and subcortical structures that ultimately modulate activation of the superior colliculus (SC) to initiate saccades. These decision processes involve accumulating uncertain evidence over time until reaching a bound, as in commonly used decision models like the drift-diffusion model (DDM). In primates, cortical signals consistent with DDM may be used to trigger SC bursts to initiate decision-indicating saccades. More flexibility in this process, particularly as related to decision bounds, can be achieved with inhibitory inputs from outside the corticocollicular pathway. We hypothesize that the zona incerta (ZI), a widely connected subcortical structure with saccade-related activity and inhibitory output to SC, contributes to SC inhibition to modulate decision making.

We measured single-unit ZI activity in two monkeys performing visual motion discrimination saccade decision tasks. The monkeys were trained to make saccades at a self-chosen time to indicate their perception of the global motion direction of a random-dot kinematogram. For each trial, the motion strength and direction were chosen randomly from five values and two directions, respectively. In the asymmetric-reward condition, one choice was paired with a large reward and the other was paired with a small reward and the reward-choice associations alternated between blocks of trials. In the equal-reward condition, both choices were paired with the same, medium-size reward. The monkeys were rewarded only for a correct choice.

In a sample of 73 neurons, ZI activity could be activated or suppressed during motion viewing and around saccade onset (collectively the deliberation period). Both activation and suppression were sensitive to choice, reward context, and expected reward size in similar percentages of neurons (~40~50%). During motion viewing, activation tended to be greater for higher-coherence trials for both choices, whereas suppression was less coherence-sensitive. Neurons showing activation were more likely to be sensitive to both reward- and visual evidence-related factors, compared to those showing suppression. We fit a DDM to choice and reaction time data and found that trial-wise variations in neural activity before saccade onset were most closely associated with bound dynamics, specifically parameters that control the maximal bound and collapse rate. These results suggest that the ZI is involved in controlling the decision bound for deliberative oculomotor decisions.

Disclosures: L. Ding: None. **K. Branam:** None. **J.I. Gold:** None.

Poster

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NIH RF1 NS118424

Title: From synaptic locus towards molecular mechanisms of song learning

Authors: *D. C. SCHREINER[1], A. LI[2], A. A. MERCER[3], J. M. PEARSON[2], R. D. MOONEY[4];
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Abstract: From synaptic locus towards molecular mechanisms of song learning
Learning by imitation is the foundation for verbal and musical expression, but its neural basis remains unclear. A juvenile male zebra finch imitates the multisyllabic song of an adult tutor in a process that depends on a song-specialized cortico-basal ganglia circuit, affording a powerful system to identify the circuit and synaptic mechanisms of imitative motor learning. An influential model proposes that plasticity at a particular set of cortico-basal ganglia synapses drives rapid learning-related changes in song before these changes are subsequently consolidated in downstream motor circuits. Nevertheless, this hypothesis was untested and the synaptic locus where learning initially occurs was unknown.
By combining a computational framework to quantify song learning with synapse-specific optogenetic and chemogenetic manipulations within and downstream of the cortico-basal ganglia circuit, we identified HVC synapses into the song-specialized basal ganglia as the premotor cortico-basal ganglia synapses that drive the acquisition and expression of rapid vocal changes during juvenile song learning and characterized the hours-long timescale over which these changes consolidate. Furthermore, transiently augmenting postsynaptic activity in the basal ganglia briefly accelerated rates of vocal change and persistently altered song without consistently driving song closer to the tutor model, suggesting a speed-accuracy tradeoff governs how quickly song can be learned. Together, these results localize the specific cortico-basal ganglia synapses that enable a juvenile songbird to learn to sing and reveal the circuit logic and behavioral timescales of this imitative learning paradigm.
Having established *where* vocal learning is initiated, ongoing work asks *how*. What are the synaptic and molecular mechanisms that convert transient activity and dopamine release into lasting synaptic change? Imaging and manipulation of postsynaptic signaling mechanisms, focusing on cAMP and CaMKIIα, are beginning to define the molecular logic that enables the learning of a complex, culturally transmitted motor skill.

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Poster

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.20/CC26

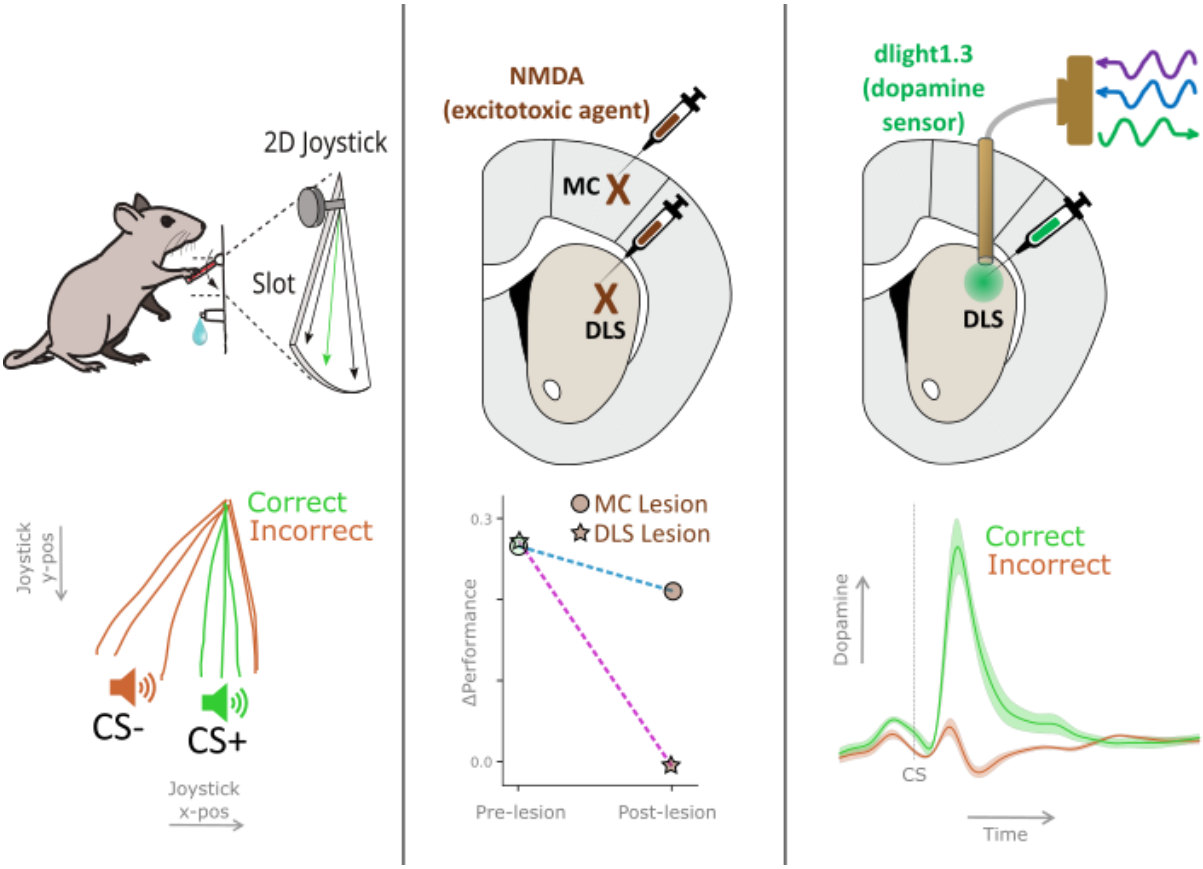
Topic: F.03. Basal Ganglia

Support: DBT-Wellcome Trust India Alliance Intermediate Fellowship (IA/I/23/2/507010)
Start-up funding from IISc

Title: NEURAL MECHANISMS OF TRIAL-AND-ERROR MOTOR LEARNING

Authors: ***A. MODI**[1], A. K. DHAWALE[2];
[1]Ctr. for Neurosci., [2]Indian Inst. of Sci., Bangalore, India

Abstract:



Acquiring new motor skills, such as a volleyball serve, relies on trial-and-error learning driven by simple feedback - success or failure. While prior studies have largely focused on discrete action selection (e.g., choosing between an underarm or overarm serve), far less is known about how the brain adapts continuous movement features such as angle or spin. Learning such kinematic parameters requires exploration of vast motor spaces, yet the underlying neural mechanisms remain unclear. We investigated the respective contributions of the basal ganglia (BG) and motor cortex (MC) to kinematic trial-and-error learning. Classical views propose that the BG learn which action to select, whereas MC learns movement kinematics. However, these roles have not been rigorously tested in a task that isolates kinematic adaptation from action selection. To address this gap, we developed a novel task in which rats learned to adapt the angle of joystick-pressing movements to obtain water rewards. Lesions of the sensorimotor striatum (DLS) abolished kinematic adaptation, whereas MC lesions did not. If DLS indeed mediates kinematic learning, we hypothesized that it should receive reinforcement signals. But prior studies suggest dopamine in DLS primarily encodes movement. Thus, we measured dopamine release using fibre photometry and found that it encoded both movement and reward. Importantly, reward-related signals scaled with reward rate, consistent with reward prediction error encoding. Lesioning dopamine terminals in the DLS using 6-OHDA abolished learning establishing a necessity of dopamine in the DLS for the process. Together, our results redefine the roles of BG and MC in motor learning and suggest that dopamine in DLS provides a teaching signal for kinematic adaptation.

Disclosures: A. Modi: None. **A.K. Dhawale:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.21/CC27

Topic: F.03. Basal Ganglia

Support: Aligning Science Across Parkinson's (ASAP-020572) through the Michael J. Fox Foundation for Parkinson's Research (MJFF)
NIH P51-OD011132 (Emory National Primate Research Center)

Title: Examination of aperiodic and periodic power spectral components in the primary motor cortex and the supplementary motor area during the development of parkinsonism in monkeys

Authors: *D. PITTARD[1,2], A.-C. MARTEL[1,2], T. WICHMANN[1,3,2], A. GALVAN[1,3,2];
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Abstract: Electrophysiological studies have demonstrated altered activity in cortico-basal ganglia circuits in Parkinson's disease (PD), likely due to loss of nigrostriatal dopaminergic (DA) projections. Recent knowledge suggests that changes in aperiodic and periodic spectral components reflect subcortical dysfunction associated with PD severity. Changes in aperiodic exponents reflect cortical excitability, whereas changes in periodic components reflect frequency-specific oscillations. When these changes occur in the supplementary motor area (SMA) and motor cortex (M1), and how they relate to motor symptoms remain unclear. We are examining these issues in two rhesus macaques undergoing chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. The animals performed an arm-reaching task in healthy and MPTP-treated states prior to symptom development. Local field potentials (LFPs) were recorded from the arm area of SMA and M1 during spontaneous behavior (SB) and task performance (TP) using multi-electrode arrays. Comparisons of aperiodic and periodic spectral components of bipolar LFP recordings between SB and TP were made using Wilcoxon signed-rank tests, and comparisons between disease states and brain regions were made with Mann-Whitney U tests. In the healthy state, we found lower aperiodic exponents during SB than TP in M1 ($p < 0.05$, $r_{rb} = -0.28$) and SMA ($p < 0.001$, $r_{rb} = -0.50$), with no difference between cortical regions. Peak beta amplitude was higher during SB than TP ($p < 0.001$, $r_{rb} = 0.72$), whereas M1 showed no change. Peak gamma amplitude was lower during SB in M1 ($p < 0.05$, $r_{rb} = -0.37$), higher in SMA ($p < 0.001$, $r_{rb} = 0.54$), and was lower in M1 than in SMA during SB ($p < 0.001$, $r_{rb} = 0.41$). In the asymptomatic MPTP-treated state, M1 exponent differences between SB and TP resembled those in the healthy state. Exponents were higher in M1 versus SMA during TP and in the asymptomatic versus healthy state ($p < 0.05$; $p < 0.001$). Task-related beta and gamma power changes were also preserved. M1 beta and gamma power increased in the asymptomatic state across behavioral conditions (all $p \leq 0.01$, $r_{rb} = 0.33$-0.65), whereas SMA gamma power decreased in both behavioral states (all $p < 0.001$, $r_{rb} = -0.62$ to -0.57). Differences between SB and TP suggest that aperiodic and periodic cortical activity reflect behavioral states. Differences between healthy and asymptomatic MPTP-treated states suggest that aperiodic and periodic activity changes emerge before motor impairments. These alterations may reflect compensatory shifts in neuronal excitability and spectral power during early dopamine depletion.

Disclosures: D. Pittard: None. **A. Martel:** None. **T. Wichmann:** None. **A. Galvan:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.22/Web Only

Topic: F.03. Basal Ganglia

Support: Ciencia de Frontera program (grant CF-G133) from SECIHTI.
International Brain Research Organization (IBRO) through the IBRO Parenthood Grant.
Partially supported by Vicerrectoría de Investigación y Estudios de Posgrado-BUAP 2026 (PV-828).

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Instituto de Salud Carlos III (CIBERNED CB06/05/0042).

Title: C-terminal domain of the heavy chain of tetanus toxin ameliorate lipopolysaccharide induced hemiparkinsonism in rats

Authors: *I. PARRA[1,2], J. AGUILERA[2], Y. TIZABI[3], L. MARTINEZ MENDIETA[1]; [1]Lab. de Neuroquímica, Benemérita Univ. Autónoma De Puebla, Puebla, Mexico; [2]Inst. de Neurociències (INc-UAB), Univ. Autónoma de Barcelona, Barcelona, Spain; [3]Dept. of Pharmacol., Col. of Med., Washington, DC

Abstract: Neuroinflammation is recognized as a central mechanism in Parkinson's disease (PD) pathogenesis. The C-terminal domain of the heavy-chain of tetanus toxin (Hc-TeTx) has shown neuroprotective effects in toxin-based PD models, but its efficacy in inflammatory-induced PD conditions remain unexplored. To test this possibility, we used the hemiparkinsonism model induced by central injection of lipopolysaccharide (LPS) to evaluate potential antiinflammatory effects of Hc-TeTx in adult male Wistar rats. Seven days post LPS-injection motor coordination and gait maintenance were assessed using elevated beam test. The day after, that is 8 days post LPS-injection, the cylinder test was used to assess forelimb motor asymmetry during spontaneous vertical exploration. Immediately after this test the animals were sacrificed for tissue collection. Dopaminergic degeneration was assessed by immunohistochemical quantification of tyrosine hydroxylase in *substantia nigra pars compacta*. Astroglial activation, reflective of neuroinflammation was evaluated by glial fibrillary acidic protein in the striatum. LPS administration caused forelimb motor asymmetry, which was significantly attenuated by Hc-TeTx treatment. Hc-TeTx also tended to attenuate LPS-induced dopaminergic neurodegeneration reflected by a reduced TH ipsilateral/contralateral ratio, as well as astroglial activation that was markedly increased after LPS administration. Beam test parameters showed no significant differences among groups. Although further verification is needed, current results support potential utility of Hc-TeTx in PD.

Disclosures: I. Parra: None. **J. Aguilera:** None. **Y. Tizabi:** None. **L. Martinez Mendieta:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.23/CC28

Topic: F.03. Basal Ganglia

Support: Parkinson's Foundation (PF-PRF-836910)
NINDS (R01NS101354)
Aligning Science Across Parkinson's (ASAP-020529)

Title: Dopamine and Striatal Activity in Cost-Benefit Decision Making in a Mouse Model of Parkinson's Disease

Authors: *X. ZHUANG[1], K. ROMO[2], J. LEMAK[4], A. B. NELSON[3];
[1]Univ. of California, San Francisco (UCSF), San Francisco, CA; [3]Neurol., [2]UCSF, San Francisco, CA; [4]Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract: Animals' choices are guided by the evaluation of benefits and costs of different actions. For example, people tend to discount the value of distant rewards, a phenomenon known as delay discounting. Individuals with impulsivity show a stronger preference for immediate rewards and intolerance for delays in delay discounting tasks. Impulsivity may arise from impaired evaluation of costs and/or benefits, and is seen in a number of neuropsychiatric conditions, such as attention-deficit hyperactivity disorder or substance use disorder. One example is Impulse Control Disorder (ICD), a complication of Parkinson's disease (PD) treatment. PD is characterized by degeneration of midbrain dopamine neurons and progressive motor impairment. Restoring dopamine signaling, particularly with D2/3-type receptor (D2/3R) agonists, alleviates motor impairment, but can be complicated by the development of ICD. ICD symptoms include pathological gambling, binge eating, or hypersexuality. Although increasing evidence from human and rodent studies has linked ICD to impaired delay discounting, the pathophysiological mechanisms remain poorly understood. To address this question, we have built on a mouse model of PD/ICD we developed in the lab. We applied two behavioral assays to separate the assessment of reward benefits and delay costs, as well as a delay discounting task, in which changes in cost and benefit are paired. We combined these assays with chemogenetics, *in vivo* fiber photometry of dopamine signaling, and *in vivo* electrophysiological recordings of striatal activity. First, we found that in parkinsonian mice, dopaminergic agonists drove more pronounced delay discounting, reminiscent of what has been reported in ICD patients. Using fiber photometry with the fluorescent dopamine sensor, dLight, we found that striatal dopamine encoded both reward benefits and delay costs. Using *in vivo* single-unit electrophysiology, we found that striatal medium spiny neurons (MSNs) increased firing during both reward and delay evaluation, suggesting a role in encoding benefits and costs. Additionally, chemogenetic manipulations of striatal MSNs caused greater delay discounting in parkinsonian mice. Taken together, our findings aim to reveal the precise neural mechanisms underlying disrupted encoding of costs and benefits in ICD and highlight an important role for striatal circuitry in value-based decision-making.

Disclosures: X. Zhuang: None. **K. Romo:** None. **J. Lemak:** None. **A.B. Nelson:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.24/CC29

Topic: F.03. Basal Ganglia

Support: NIH R01NS131276

Title: Regional Tau Pathology Predicts Progressive Supranuclear Palsy-Like Motor Deficits in a Mouse Model of Tauopathy

Authors: *X. LIU, S. SRIDHAR, R. B. CREED, A. B. NELSON;
Neurol., Univ. of California San Francisco, San Francisco, CA

Abstract: Progressive Supranuclear Palsy (PSP) is a rapidly progressive neurodegenerative disease characterized by early deficits in balance, gait, and eye movements. Postmortem analysis shows pathological accumulation of phosphorylated tau in many brain areas in people with PSP, but how neural circuits vulnerable to tau contribute to disease phenotypes remains poorly understood. In this study, we examined the relationship between regional tau burden and PSP-relevant behavioral dysfunction in a P301S tau transgenic mouse model.

To investigate the relationship between tau pathology and PSP-associated behavioral deficits, we used 5-month-old P301S tau transgenic mice and quantified phosphorylated tau using AT8 immunohistochemistry. At 5 months of age, P301S mice display show motor deficits, including changes in gait, balance, and eye movements as compared to wild-type controls. At this time point, pathological tau can be found in multiple brain areas. We examined whether tau burden within specific motor and oculomotor circuits was associated with PSP-relevant behavioral phenotypes.

Consistent with previous reports, AT8-positive tau pathology was observed throughout cortical, basal ganglia, brainstem, and cerebellar regions. To determine whether regional tau burden was associated with PSP-relevant behavioral deficits, we quantified pathology across candidate motor and oculomotor structures, including the motor cortex, medial superior colliculus (SCm), zona incerta (ZI), subthalamic nucleus (STN), substantia nigra pars reticulata (SNr), cuneiform nucleus (CUN), pedunculopontine nucleus (PPN), vestibular nuclei (VN), and deep cerebellar nuclei (DCN). The deficits in reflexive saccades in the P301S tau model prompted a more focused analysis of oculomotor regions in the midbrain and brainstem. We quantified tau burden within the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), interstitial nucleus of Cajal (INC), paramedian pontine reticular formation (PPRF), abducens nucleus, and oculomotor nucleus, key structures involved in the generation and control of eye movements. Notably, tau burden in the vestibular nuclei, PPN, DCN, and ZI correlated with changes in rotarod performance, gait kinematics, or both. Together, these findings suggest that specific brainstem motor and oculomotor circuits may exhibit vulnerability to tau pathology and provide potential anatomical targets for understanding the neural basis of PSP symptoms.

Disclosures: X. Liu: None. **S. Sridhar:** None. **R.B. Creed:** None. **A.B. Nelson:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.25/CC30

Topic: F.03. Basal Ganglia

Support: NIH Grant K99NS142566
NIH Grant K00NS108458
BWF Grant A139941

Title: Expression of Mutant Human Tau in the SNr drives pathological, oculomotor and locomotor phenotypes in mice

Authors: *R. B. CREED[1], S. C. HARRIS[2], S. SRIDHAR[4], F. P. MANFREDSSON[6], F. A. DUNN[5], A. B. NELSON[3];
[1]Neurol., Univ. of California, San Fransisco, San Francisco, CA; [2]Ophthalmology, [3]Neurol., UCSF, San Francisco, CA; [4]Neurol., [5]Opthalmology, Univ. of California, San Francisco, San Francisco, CA; [6]Translational Neurosci., Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Progressive Supranuclear Palsy (PSP) is a neurodegenerative disease that affects movement, behavior, and cognition. Due to an overlap in symptoms with Parkinson's disease, PSP is considered an atypical parkinsonian disorder, but PSP patients have distinct clinical and pathological features. Clinically, PSP patients have early gait abnormalities, frequent falls, gaze palsy, and tend not to respond to dopamine replacement therapy. Pathologically, aggregated Tau protein accumulates in the brain of PSP patients. As in other neurodegenerative disorders, a combination of cellular dysfunction and cell loss is believed to drive disease symptoms. However, a lack of animal models for PSP has hindered investigation of the causal links between neuropathology, cellular and circuit dysfunction, and symptoms. Here, we have utilized two different approaches to modeling tauopathy to test whether Tau pathology is sufficient to recapitulate key PSP phenotypes in mice. The first model is a transgenic mouse expressing human mutant (P301S) tau. The second model uses AAV to target human doubly-mutant (P301L/S320F) tau to the substantia nigra, pars reticulata (SNr), and area of early Tau pathology in PSP. All mice were run through a battery of locomotor tests: (1) open field and (2) rotarod to assess gross locomotion and balance, (3) linear track to assess gait and coordination. A subset of mice were headfixed for assessment of saccadic eye movements. We also performed *in vivo* single-unit electrophysiology in the SNr of separate cohorts of mice undergoing these behavioral tests. We find Tau transgenic mice have impaired open field locomotion and poor balance on the accelerating rotarod test. Additionally, Tau mice show impaired gait kinematics. Furthermore, we see that overexpression of Tau in both of our models results in eye movement impairments, including difficulty with vertical saccades. Locomotor impairments parallel aberrant neuronal activity in the SNr. Together, these findings indicate Tau pathology is sufficient to drive locomotor and oculomotor impairments in mice, reproducing key PSP clinical phenotypes. These models provide a platform to further investigate the changes in neural structure and function that drive the behavioral deficits seen in disease.

Disclosures: R.B. Creed: None. **S.C. Harris:** None. **S. Sridhar:** None. **F.P. Manfredsson:** None. **F.A. Dunn:** None. **A.B. Nelson:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.26/DD1

Topic: F.03. Basal Ganglia

Support: NIH Grant R01AA027768
NIH Grant U01AA025932
NIH Grant R01AA030293

Title: Prenatal fentanyl exposure produces sex-dependent alterations and enhances alcohol-related behaviors in adult mice

Authors: *V. VIERKANT[1], X. XIE[2], J. WANG[3];
[1]Neurosci. and Exptl. Therapeut., Texas A&M Univ. Syst. Hlth. Scien Neurosci. and Exptl. Therapeut., College Station, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; [3]Dept. of Neurosci. & Exptl. Therapeut., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: Prenatal opioid exposure is an increasing public health concern, but how developmental fentanyl exposure affects adult vulnerability to alcohol-related behaviors remains poorly understood. Here, we examined whether prenatal fentanyl exposure (PFE) produces persistent, sex-dependent behavioral alterations and increases alcohol-related behaviors in adult mice. Pregnant dams received fentanyl during gestational days 11-19, and adult offspring were tested for body weight, spontaneous locomotor activity, alcohol consumption and preference in a two-bottle choice procedure, and alcohol-cue responding in a Pavlovian alcohol-conditioning paradigm. PFE produced persistent behavioral effects that differed by sex. Male PFE offspring exhibited reduced adult body weight relative to controls, whereas female PFE offspring showed increased locomotor activity. In alcohol-related assays, PFE increased alcohol preference in males and enhanced Pavlovian conditioned responding to alcohol-associated cues, reflected by increased licking during alcohol-cue presentations. These results indicate that developmental fentanyl exposure produces long-lasting, sex-dependent behavioral changes and enhances behavioral sensitivity to alcohol-related cues and outcomes. Together, our findings suggest that prenatal fentanyl exposure may increase susceptibility to alcohol-related behaviors in adulthood and support future studies to identify the neural adaptations through which early opioid exposure elevates risk for substance use disorders.

Disclosures: V. Vierkant: None. **X. Xie:** None. **J. Wang:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.27/DD2

Topic: F.03. Basal Ganglia

Support: R01AA027768
U01AA025932
R01AA030293

Title: Fentanyl Withdrawal Alters Striatal Cholinergic Interneuron Excitability and Reward-Related Behavioral Flexibility

Authors: *L. QI[1], X. XIE[2], J. WANG[3];
[1]Texas A&M Univ., Bryan, TX; [2]Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; [3]Dept. of Neurosci. & Exptl. Therapeut., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX

Abstract: Opioid use disorder is often accompanied by persistent drug-associated memories and impaired behavioral flexibility, but the striatal mechanisms that support these adaptations remain unclear. Cholinergic interneurons (CINs) regulate striatal acetylcholine signaling, action-outcome learning, and adaptive behavioral updating, and their activity is influenced by neuromodulatory and stress-related inputs, including corticotropin-releasing factor (CRF)-linked circuits. Here, we examined whether repeated fentanyl exposure and withdrawal alter CIN excitability and reward-related flexibility. Animals received repeated fentanyl or saline treatment and were tested in conditioned place preference (CPP) and reversal learning tasks to assess fentanyl-associated reward memory and behavioral updating. To determine whether withdrawal changes CIN function, we performed ex vivo whole-cell current-clamp recordings from genetically identified CINs in acute striatal slices. Fentanyl-exposed animals showed persistent CPP-associated behavioral changes and altered performance during reversal learning, indicating that fentanyl history disrupts reward-guided behavioral flexibility. In acute slices, CINs from fentanyl-withdrawn animals displayed altered intrinsic excitability compared with saline controls, including changes in spontaneous firing and current-evoked firing responses. These findings suggest that fentanyl withdrawal shifts the activity state of striatal CINs. Ongoing experiments are testing whether CRF-linked signaling contributes to these withdrawal-associated changes. Together, our results support a model in which fentanyl withdrawal disrupts striatal CIN excitability and may impair acetylcholine-dependent regulation of reward learning and behavioral flexibility. This work identifies CIN firing as a potential cellular mechanism linking opioid withdrawal to persistent drug-associated behavior and cognitive inflexibility.

Disclosures: L. Qi: None. **X. Xie:** None. **J. Wang:** None.

Poster

PSTR061: Systems Behavior

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR061.28/DD3

Topic: F.03. Basal Ganglia

Support: NIH Grant R01AA027768
NIH Grant U01AA025932
NIH Grant R01AA030293

Title: Input-Specific Regulation of Alcohol Self-Administration and Extinction by Cortical and Thalamic Projections to striatal iMSNs

Authors: *J. WANG[1], V. VIERKANT[2], Z. LI[2], Y. HUANG[2], X. XIE[2], R. CHEN[2], J. YANG[3]; [1]Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; [2]Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; [3]Vet. Integrative Biosci., Texas A&M Univ., College Station, TX

Abstract: Alcohol use disorder (AUD) is characterized by persistent alcohol seeking and impaired behavioral inhibition. The dorsomedial striatum (DMS) regulates alcohol-related actions through direct- and indirect-pathway medium spiny neurons, yet the input-specific role of DMS indirect-pathway medium spiny neurons (iMSNs) in alcohol seeking and extinction remains unclear. Here, we used D2-Cre rats, operant alcohol self-administration, projection- and cell-type-specific optogenetics, viral tracing, and slice electrophysiology to determine how cortical and thalamic inputs to iMSNs regulate alcohol-seeking behavior. Acute optogenetic excitation of DMS iMSNs reduced alcohol seeking, deliveries, intake, and magazine entries, whereas chronic alcohol drinking reduced iMSN excitability while increasing dMSN excitability. Inducing long-term potentiation (LTP) at medial prefrontal cortex (mPFC)-to-iMSN synapses produced a sustained, N-methyl-D-aspartate receptor-dependent suppression of alcohol seeking and taking, with limited effects on sucrose seeking. During extinction, glutamatergic transmission onto iMSNs was strengthened, and optogenetic inhibition of iMSN output delayed extinction and enhanced reinstatement. Monosynaptic tracing identified the central medial nucleus (CM) of the thalamus as a major source of input to DMS iMSNs, and extinction selectively potentiated CM-to-iMSN AMPAR-mediated transmission. Inhibiting CM neurons disrupted alcohol extinction, promoted reinstatement, and increased compulsive-like responding for quinine-adulterated alcohol without altering sucrose extinction or taste sensitivity. Finally, optogenetic induction of long-term depression (LTD) at CM-to-iMSN synapses impaired extinction learning and weakened established extinction memory. These findings identify DMS iMSNs as a behavioral brake on alcohol seeking and reveal input-specific functions of mPFC-to-iMSN and CM-to-iMSN circuits in suppressing alcohol seeking and supporting extinction. Enhancing these iMSN-centered circuits may offer a strategy for reducing alcohol relapse.

Disclosures: J. Wang: None. **V. Vierkant:** None. **Z. Li:** None. **Y. Huang:** None. **X. Xie:** None. **R. Chen:** None. **J. Yang:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.01/DD4

Topic: F.04. Voluntary Movements

Title: Target Interception in Stage Combat

Authors: *B. BROCKSHUS[1], E. L. STEGEMOLLER[2];
[1]Kinesiology, Louisiana Tech. Univ., Ruston, LA; [2]Kinesiology, Iowa State Univ., Ames, IA

Abstract: Stage combat is a multifaceted movement discipline in which violence is simulated for an audience. Fundamental to the practice are functional skills and abilities such as target interception, locomotion, movement sequencing, and spatial awareness. These skills and abilities have not been studied in the context of stage combat, so appropriate measures must be identified. This study used a novel target interception task wherein a prop quarterstaff was swung in a cutting motion at a stationary target. Motions of the staff and the mover's effectors were captured using inertial measurement units placed on the staff, forearm, arm, and sacrum. Twenty-eight participants (30.25 ± 1.87 SEM years, 15 female) each performed seven cutting movements. Across the seven movements, movement variability decreased in the forearm Y-axis ($t = 2.52$, $p = 0.018$), arm Z-axis ($t = 2.33$, $p = 0.028$), and arm X-axis ($t = 2.24$, $p = 0.033$). Movement duration ($t = -1.16$, $p = 0.258$) and duration variability ($t = 1.067$, $p = 0.295$) did not change. It was hypothesized that movement variability and duration variability would decrease across the seven movements as a result of familiarization with the task and on-line motor learning. The first hypothesis was partially supported. This novel target interception task may be appropriate for the investigation of motor learning in the context of stage combat. Alternate measures of motion analysis such as infrared camera with markers or markerless camera systems may also be appropriate and should be investigated. Use of an active target may better simulate the stage combat context. Further study is warranted.

Disclosures: B. Brockshus: None. **E.L. Stegemoller:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.02/Web Only

Topic: F.04. Voluntary Movements

Support: JSPS KAKENHI 24K23823

Title: Error-size processing differs between visually and memory-guided tasks in visuomotor adaptation

Authors: *K. NUMASAWA[1], R. HIRANO[2], S. ONO[1,3];
[1]Inst. of Hlth. and Sport Sci., [2]Grad. Sch. of Comprehensive Human Sci., [3]Advanced Res. Initiative for Human High Performance (ARIHHP), Univ. of Tsukuba, Ibaraki, Japan

Abstract: Accurate movements are maintained through motor adaptation, which enables the motor system to adjust movements in response to sensory errors. Recent studies have reported that the characteristics of motor adaptation differ depending on task context, such as between visually guided movements, in which movements are initiated in response to visible target information, and memory-guided movements, in which movements are guided by remembered target information. However, the mechanisms underlying these differences are not yet fully understood. Although motor adaptation studies tend to focus on how adaptation is retained, error processing is also a crucial component of adaptation. We hypothesized that error processing differs between visually guided and memory-guided movements and tested this hypothesis in the present study. The apparatus consisted of a digitized tablet to capture hand movements and a monitor to display visual stimuli. Participants were required to control a cursor on the monitor synchronized with a stylus. They sat facing the monitor and were asked to move the cursor from a start circle to a target. In the visually-guided task, participants started reaching movements immediately when a target appeared. In the memory-guided task, they were asked to memorize the position of the target and reach toward the memorized position. In Experiment 1, we examined the single-trial motor correction to the clamped feedback, which was presented at a fixed location relative to a target. The clamped feedback with randomly selected clamp sizes (0°, ± 2°, ± 4°, ± 8°, and ± 16°) was presented. Our results showed a significant interaction between the clamp size and the task conditions (visually vs memory). For small errors, correction responses were larger in the visually-guided task, whereas for large errors, correction responses were larger in the memory-guided task. Bayesian sensory integration models suggested that the visual uncertainty could be dissociated by the task conditions, which influence motor adaptation. In Experiment 2, we observed the gradual adaptation to a visuomotor rotation by 0.2° per trial up to 20°. The result showed greater adaptation in the visually-guided task than in the memory-guided task. These findings from two experiments indicate that the task type modulates error processing, which in turn influences the rate and magnitude of motor adaptation. Understanding such task-dependent error processing may contribute to the development of more effective rehabilitation and training strategies.

Disclosures: K. Numasawa: None. **R. Hirano:** None. **S. Ono:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.03/DD5

Topic: F.04. Voluntary Movements

Support: NIH Grant R01DC020707
NIH Grant F99AG088438

Title: Alpha and beta event-related desynchronization during speech planning dissociate auditory-motor adaptation and syllable sequence learning differently in younger and older adults

Authors: *H. WANG[1,2], L. MAX[2];
[1]Univ. of California, San Francisco, San Francisco, CA; [2]Univ. of Washington, Seattle, WA

Abstract: Aging affects the neural substrates and sensorimotor processes underlying speech motor control, and aging-related neurodegenerative diseases can lead to severe motor speech impairments. Yet efforts to incorporate motor learning mechanisms into motor speech treatment have been impeded by a lack of empirical data on how aging affects different forms of speech motor learning at both behavioral and neural levels. We recorded EEG from younger adults (n=21, mean age=21.1 years) and older adults (n=21, mean age=68.9 years) as they completed an auditory-motor adaptation task with first formant (F1) perturbation and a syllable sequence task. Both tasks were designed to include repeated short learning phases to maximize the number of trials where learning occurred. Alpha and beta event-related desynchronization (ERD) during the pre-speech planning period were examined as potential learning-related neural markers in each task.
Both groups showed significant F1 adaptation with no age difference in adaptation magnitude, consistent with prior findings of preserved implicit sensorimotor adaptation in aging. In the syllable sequence learning task, older adults showed significant accuracy improvement in early trials whereas younger adults did not, which may reflect a performance ceiling in the younger group. Both groups increased speech rate across trials, though younger adults showed descriptively greater speech rate improvement in early learning trials, consistent with prior reports of negative effects of aging on explicit motor sequence learning.
EEG analyses revealed robust alpha and beta ERD during pre-speech planning in both tasks and both age groups. In the adaptation task, no group or learning phase (early vs. late) differences emerged in alpha or beta power. In the syllable sequence learning task, older adults exhibited descriptively stronger beta ERD than younger adults, which may reflect greater cognitive resource recruitment during this task. Younger adults showed stronger alpha ERD in early versus late learning phases whereas older adults did not, possibly reflecting a transition from a cognitively intensive early learning phase to a more automatized late learning phase in younger adults but not in older adults. These findings reveal age-related differences in the oscillatory dynamics of syllable sequence learning and may suggest new directions for research on the effects of aging on speech and nonspeech motor learning.

Disclosures: H. Wang: None. **L. Max:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.04/DD6

Topic: F.04. Voluntary Movements

Title: Ballistic goal-directed training enhances force endpoint control in older adults

Authors: M. TRAPEZANIDOU[1], G. CHALATZOGLIDIS[1], B. YACOUBI KEYHANI[2], F. ARABATZI[1], *E. A. CHRISTOU[2];
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Abstract: Age-related declines in the endpoint control of ballistic goal-directed contractions have been linked to impaired gait performance, including increased gait variability, a strong predictor of falls in older adults. However, whether endpoint control can be improved through targeted training remains unknown. Therefore, the aim of this study was to determine whether ballistic goal-directed plantarflexor training enhances endpoint control in older adults and to identify the neuromuscular adaptations underlying any observed improvements. Twenty-two older adults (72±6 years) participated in this study. Thirteen participants completed a ballistic goal-directed training intervention consisting of eight sessions of 100 plantar flexions (EXPERIMENTAL group). Participants were instructed to match a force target (30% MVC) accurately and as fast as possible. The other 9 participants did not participate in any form of training and acted as the CONTROL group. All participants attended three experimental sessions (baseline, 1-week, and 2-weeks post-intervention), during which they performed 3 sets of 10 ballistic goal-directed plantar flexions at 30% MVC. Endpoint control was assessed by quantifying the peak force error (PFE), Time to Peak Force (TPF), peak force and TPF variability (CV PF, CV TPF). Muscle activity was recorded using surface EMG electrodes on Gastrocnemius Medialis and Lateralis (MG, LG), Soleus (SOL), and Tibialis Anterior (TA) muscles. After one week of training, the EXPERIMENTAL group significantly reduced peak force error (PFE), the coefficient of variation of peak force (CV PF) and the time to peak force (TPF), whereas no changes were observed in the CONTROL group. These improvements were maintained after the second week of training in the EXPERIMENTAL group, while the CONTROL group continued to exhibit no changes. These changes were accompanied by alterations in muscle activation and coordination patterns. TPF reductions were largely predicted by reductions in LG time-to-peak EMG and antagonistic (TA-LG Overlay) coactivation. CV PF reductions were primarily predicted by changes in SOL time-to-peak EMG variability and TA Area variability. These findings demonstrate that ballistic goal-directed training improves endpoint control in older adults by reducing force error, force variability, and time to peak force. These gains appear to be mediated by adaptations in neuromuscular activation and intermuscular coordination. Collectively, the results provide novel evidence that ballistic training enhances the accuracy, consistency, and speed of force production in older adults, with potential implications for reducing fall risk.

Disclosures: M. Trapezanidou: None. **G. Chalatzoglidis:** None. **B. Yacoubi Keyhani:** None. **F. Arabatzi:** None. **E.A. Christou:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.05/DD7

Topic: F.04. Voluntary Movements

Title: A Shared-Error Framework for Implicit and Explicit Motor Learning

Authors: *H. SOROUSHI, Y. LEI;
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Abstract: Human sensorimotor adaptation is commonly described as the combined effect of explicit strategy and implicit recalibration. However, these processes may not operate independently; instead, they may compete for a shared task-error signal. In this study, we investigated this interaction using a KINARM-based reaching task. Twenty healthy participants were recruited and assigned to either a sham group or an active cue group. The sham group included participants who performed the task without directional guidance. The active group included participants divided into three cue conditions, in which an arrow was displayed on the screen to guide movement at 45°, 35°, or 25°.Importantly, the visuomotor rotation was centered at 45° across the active conditions. In addition to this baseline rotation, a sum-of-sines sinusoidal perturbation was continuously added to the rotation angle. This perturbation served two main purposes. First, it introduced controlled trial-to-trial variability, allowing better detection and modeling of whether behavior was more likely dominated by explicit strategy or implicit adaptation. Second, it allowed us to examine how motor learning responds when the imposed rotation contains ongoing induced error over time.By comparing sham performance with different cue-guided active conditions, this experiment aims to determine how explicit guidance shapes the use of task error and how this, in turn, influences implicit adaptation. This behavioral framework provides a foundation for estimating the interaction between explicit and implicit learning states and for understanding how the sensorimotor system adapts when the error environment is both biased and dynamically perturbed.

Disclosures: H. Soroushi: None. **Y. Lei:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.06/DD8

Topic: F.04. Voluntary Movements

Support: 2024 Virginia Commonwealth University Quest Fund
2025 Virginia Commonwealth University Parkinson's and Movement and Disorder Center (PMDC) Pilot Grant

Title: Canonical Visuomotor Adaptation and Lateralization Generalize to Three-Dimensional Reaching in Immersive Virtual Reality

Authors: N. DRUCK[1], N. YAGHOUBI[2], P. E. PIDCOE[1], B. DEXHEIMER[1], ***D. J. KRUSIENSKI**[1];
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Abstract: Visuomotor rotation (VMR) paradigms have been widely used to study motor adaptation and inter-limb transfer; establishing behavioral signatures including rapid initial error, gradual correction, after-effects during washout, and lateralization between the dominant and non-dominant arms. These signatures, however, are derived almost entirely from planar two-dimensional (2D) reaching; but generalization to naturalistic three-dimensional (3D) movements that mimic everyday behavior (subject to biomechanical and perceptual demands) remains unclear. Therefore, we implemented a 3D VMR reaching task in immersive virtual reality, pairing classical kinematic measures with 3D analogs of established adaptation metrics. Fifteen right-handed adults (mean age 22.3) performed seated point-to-point reaches to targets on a virtual tabletop using an HTC VIVE Pro 2, with 3D hand position sampled at 90 Hz. Each completed baseline, rotation (a counterclockwise VMR of 10, 20, or 30 degrees applied for 100 reaches per arm), and washout phases, with arm order counterbalanced across groups. We quantified movement time, peak velocity, percent time to peak velocity, and spectral arc length (smoothness), alongside two adaptation analogs: Euclidean Trajectory Deviation (ETD) and End Point Accuracy (EPA). Group differences across twelve valid participants were assessed with FDR-corrected t-tests. Across participants, the rotation induced initial trajectory and endpoint errors that gradually decreased with adaptation and produced after-effects during washout, mirroring 2D findings. Arm order strongly shaped performance: participants who began the task with their ND arm adapted more rapidly, achieving significantly lower ETD and EPA (both $p<0.001$ during rotation) and faster, smoother, more efficient movements that persisted into washout ($p<0.001$). These lateralization effects were evident in both trajectory-level adaptation and the timing and smoothness of execution. Together, these results indicate that the canonical signatures of 2D visuomotor adaptation, including lateralization, largely generalize to 3D reaching despite greater complexity. Immersive 3D VR thus offers a promising platform for studying motor learning and for assessing and training naturalistic reaching in rehabilitation.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.07/DD9

Topic: F.04. Voluntary Movements

Support: Presidential Fellowship, University of South Carolina

Title: Effect of target difficulty on the learning of individual components of whole-arm motor sequence task

Authors: T. LEE, C. SMITH, T. HERTER, *J. C. STEWART;
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Abstract: Background: Learning of a motor sequence that requires whole-arm movements includes changes in both spatial and temporal aspects of reaching. Individual components of the sequence may have different levels of difficulty based on factors such as target distance and inertial demands. However, it is not known if target difficulty impacts the learning of the components of a motor sequence task. Thus, the purpose of this study was to investigate the effects of target difficulty on the learning of the individual components of a motor sequence task that required three-dimensional (3D) reaching movements. **Methods:** Twenty-four right-hand dominant young adults completed a sequence task that required 3D reaching movements on two consecutive days with either the left (n=12) or right (n=12) arm. The difficulty of each target in the sequence was defined based on a combination of Fitts' Index of Difficulty (ID) and direction-specific inertial demands. Performance was assessed by movement time, hand path distance, and peak velocity. Acquisition was assessed based on changes in performance on Day 1 with a linear mixed model. Learning was defined as change in performance from early Day 1 (first nine trials) to early Day 2 (first nine trials). To determine whether learning differed based on target difficulty, normalized relative change values ($\Delta \times 100$) were compared between the easiest (ID=2.42/Low Inertia) and hardest (ID=3.78/High Inertia) targets. **Results:** Movement time decreased for all targets regardless of difficulty or arm ($\beta < -0.006$, $P < 0.01$). Hand path distance also decreased across targets in both arm groups ($\beta < -0.019$, $P < 0.05$). Peak velocity tended to decrease over trials in the left arm group but increase or stay the same in the right arm group ($\beta < 0.032$, $P < 0.01$). Early practice (first nine trials) was characterized by faster movement time, straighter hand paths, and lower peak velocity suggesting individuals initially focused on spatial performance instead of movement speed. Performance gains were retained on Day 2 across variables and targets ($P < 0.05$). The normalized performance values were not significantly different between the easiest and hardest targets ($P > 0.05$). **Conclusion:** Participants showed similar acquisition and learning of individual components of the motor sequence regardless of target difficulty. Performance gains in the left arm group were primarily through changes in the hand path suggesting a focus on the spatial aspects of reach control. The impact of target difficulty when learning tasks that require whole-arm reach movements may be relevant in the rehabilitation of individuals with reach control deficits such as stroke.

Disclosures: T. Lee: None. **C. Smith:** None. **T. Herter:** None. **J.C. Stewart:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.08/DD10

Topic: F.04. Voluntary Movements

Support: ERC Consolidator Grant EP/X040372/1
EPSRC Grant EP/W004062/1
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Title: Sensory and Motor Building Blocks of an Extra Robotic Digit Representation

Authors: *L. DOWDALL[1,3], E. AMORUSO[4,2], G. DOMINIJANNI[5,2], M. MOLINA-SANCHEZ[6,3], S. SHOKUR[8,9], S. MICERA[10,9], J. DIEDRICHSEN[11], D. CLODE[7,12], T. R. MAKIN[3,2];
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Abstract: Augmentation technologies raise fundamental questions about how the nervous system can adapt to integrate and represent novel body parts. We asked whether the neural representation of a supernumerary robotic digit (the "Third Thumb") is exclusively dependent on the body parts controlling and sensing the device, or whether an emergent, more independent representation is observed.
The Third Thumb is controlled by pressure sensors under the big toes, and is worn on the hand, with the user 'naturally' receiving sensory feedback on the side of their palm during movement. Using fMRI, we asked whether the Third Thumb's representation is more than the sum of its controller movement (the toes) and effector sensory consequences (on the hand). Following short term training, 24 novice users performed a tapping task in the MRI scanner, wearing and actively controlling an MRI compatible Third Thumb. In separate conditions, participants would i) move the Third Thumb, ii) move their toes (no Thumb movement) and iii) passively experience the Third Thumb moving on its own on the hand (no toe movement). This allowed identification of the specific toe-controller and sensory-feedback activity patterns to then explore how this information combines to represent the Third Thumb. Through a linearity analysis, we found the Thumb is successfully represented in primary motor cortex (M1) hand area as a linear sum of toe-controller and Thumb feedback signals.
To explore how this changes with expertise, the fMRI paradigm was repeated with trained Third Thumb users (9 days of training, n=30). In M1's hand area we found a significant increase in activity when both actively controlling the Third Thumb, and when just receiving its sensory feedback. This implies retuning to the Thumb's sensory and motor components by the biological hand area as it becomes integrated into the participants' motor plans. When considering the components combining to produce the Third Thumb's neural representation, linearity analysis indicated that the combination of the toe-controller and Thumb feedback signals was no longer sufficient to explain the Third Thumb's multivariate pattern. These preliminary findings imply that an independent representation of the Third Thumb may be emerging following long term training.
In sum, we found while the initial representation of a novel body part is dependent on the sensory and motor components comprising motor control, unique information beyond this summation becomes available with extended training, implying a novel, independent representation. This has implications for our understanding of how the brain learns to represent artificial limbs and integrate them with our body.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.09/DD11

Topic: F.04. Voluntary Movements

Support: NIH Grant R01 NS131552
NIH Grant R01 NS131552

Title: Sensorimotor adaptation without movement execution: shared and distinct signatures across movement, planning, and observation

Authors: *Y. CHEN[1], O. A. KIM[2], S. D. MCDOUGLE[3], J. A. TAYLOR[1];
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[3]Psychology, Yale Univ., New Haven, CT

Abstract: Sensorimotor adaptation is believed to result from sensory-prediction errors that are formed when an executed movement produces an unexpected sensory outcome. However, adaptation has also been shown to occur following observation of an error (Mattar & Gribble, 2005) and more recent work suggests that movement planning alone is sufficient to drive recalibration (Kim et al., 2022). These findings are at odds with typical internal forward model frameworks that presuppose the necessity of movement execution signals. To reconcile these findings, we asked whether adaptation driven by observation or movement planning alone is behaviorally similar to adaptation driven by movement execution. We first tested whether observing an error can induce implicit recalibration in an online visuomotor rotation task in which an error-clamp paradigm was used to minimize contributions from explicit strategies and other learning processes (Exp. 1). We then asked whether planning- and observation-based learning exhibit the same behavioral signatures as movement-based learning across acquisition, accumulation, and retention (Exps. 2-3). We found that exposure to a simulated error in the observation condition, without any cue to prepare a movement, was sufficient to drive significant single-trial adaptation. This effect was smaller than adaptation following movement execution but comparable to adaptation following movement planning alone. However, when errors were presented repeatedly, planning and observation produced minimal, non-accumulating learning, in contrast to the robust accumulation observed with movement execution. Finally, we characterized the retention of an established adapted state. Because planning and observation do not themselves produce reliable accumulation, we first induced adaptation using movement with error-clamp feedback and then measured its retention over a period approximating 60 s of continuous movement, planning, or observation. Planning and observation retained most of the induced adaptation, whereas movement produced markedly faster decay, consistent with each

no-feedback movement actively washing out the adapted state. Taken together, planning and observation produced similar adaptation signatures that diverged from the adaptation following movement in distinct ways. A key open question is whether observation drives learning through a generic process that provides a common baseline for movement- and non-movement-based learning, or whether observing an error prompts the covert, retrospective generation of a motor plan-like signal, engaging a similar mechanism as the planning condition.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.10/DD12

Topic: F.04. Voluntary Movements

Support: R01 NS139424

Title: Left posterior parietal cortex involvement in left-arm adaptation and interlimb transfer

Authors: *H. HIBINO[1], B. UITZ[1], J. KOGAN[1], C. GUCKIAN[1], T. MURPHY[3], M. YAROSSI[2,1], R. L. SAINBURG[5,4], E. TUNIK[1];
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Abstract: Visuomotor rotation adaptation is attributed to memory-driven updating of a motor plan and visuo-proprioception remapping initiated by sensory mismatch during movement. We previously reported that left posterior parietal cortex (PPC) involvement in right-arm adaptation and interlimb transfer of learning occurs during movement; however, whether such a timing-specific contribution is generalizable to left-arm adaptation and interlimb transfer is unclear. Here, we causally probed left PPC involvement in left-arm adaptation and interlimb transfer by delivering transcranial magnetic stimulation (TMS) at pre-movement or peri-movement during visuomotor rotation adaptation. Healthy right-handed subjects were randomly assigned to one of three TMS groups: No TMS (n=10), pre-movement TMS (n=8), and peri-movement TMS (n=8) following IRB-approved informed consent. All subjects performed center-out reaching movements to eight targets over five conditions: Right-Arm Baseline, Left-Arm Baseline, Left-Arm Adaptation (Adaptation), Right-Arm Transfer (Transfer), and Right-Arm Washout (Washout). The cursor was veridically matched to hand motion during Baseline and Washout and deviated 30◦ counterclockwise during Adaptation and Transfer. During Left-Arm Baseline and Adaptation, TMS was delivered 50ms after target presentation (pre-movement) or when the hand was 8cm from the center (peri-movement). Reach errors were defined as the absolute angular difference between the center-to-target and center-to-hand vectors at peak acceleration

(|AE|). Baseline-centered |AE| (|AE|Δ) was calculated by subtracting the mean |AE| of the last 16 trials of a given reach movement (e.g., Left-Arm Baseline for Adaptation, Right-Arm Baseline for Transfer and Washout) from each trial. We compared |AE|Δ between groups in the 1st and 2nd Half of Adaptation, Transfer, and Washout. While all three groups had comparable |AE|Δ during Adaptation, reaching error during Transfer and Washout was group dependent. Despite the absence of stimulation during Transfer, peri-movement TMS had significantly lower |AE|Δ than pre-movement TMS ($p < 0.001$) and a marginally significant trend toward lower |AE|Δ than No TMS ($p = 0.056$). Additionally, peri-movement TMS had lower |AE|Δ than No TMS ($p < 0.05$) and pre-movement TMS ($p < 0.01$) in the 2nd Half of Washout. These results suggest that the contribution of left PPC to interlimb transfer may occur during the movement phase of left-arm adaptation. Together with our previous results, the contribution of left PPC to initial adaptation seems to be effector-dependent, whereas its contribution to interlimb transfer may be effector-independent.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.11/DD13

Topic: F.04. Voluntary Movements

Support: NIH Grant 1R01NS096083
NSF CAREER 1352632
NSF GRFP DGE 2040434

Title: When less error is more effort: Penalizing accuracy with effort does not compromise or assist motor adaptation

Authors: *R. M. MARBAKER[1,2], A. A. AHMED[2];
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Abstract: Across motor learning modalities, error reduction is concurrent with reductions in metabolic cost . Though the cost reduction can be attributed to reduced muscular co-activation, it is unclear what causal role effort is playing in the learning process. Is error reduction in learning partly driven by a concomitant drive to reduce effort or is the pattern of decreasing metabolic cost only an artifact? We designed a task to manipulate the learning-related effort landscape to clarify whether a predisposition for effort minimization contributes to gradual error correction during motor learning.
In an unrewarded visuomotor rotation task, we tested three groups (n = 63, 21 per group) assigned to different viscous movement resistance effort landscapes. A control group

experienced low resistance (2Ns/m) that did not change with error, while two experimental groups experienced error-dependent resistance: error-congruent resistance penalized high error with high effort and error-incongruent resistance penalized high accuracy (low error) with high effort. We predicted that participants in the error-congruent effort group would learn faster than controls because error and effort minimization objectives were aligned. Reciprocally, we predicted that participants in the error-incongruent effort group would learn more slowly because error and effort minimization objectives were at odds.
Participants learned a 30deg visuomotor rotation where movements were made through a viscous field opposing the direction of movement (f = -bv). The damping gain, b, was updated using a group-specific function of reach error. Damping was updated within a trial based on the initial angular reach error and ranged between 2 and 37 Ns/m for the error-congruent and -incongruent groups based on a sigmoid function with ± 0.1 slope, ensuring that groups were sharply penalized for error and accuracy respectively.
Neither effort landscape manipulation altered the learning process: all three groups learned at a similar rate ($\chi^2(2) = 0.94$, $p = 0.627$) and had similar error plateaus (last 30 trials $\chi^2(2) = 0.31$, $p = 0.89$). Early on, groups moved at similar speed ($F(2,60) = 1.9$, $p = 0.16$), but the congruent group moved progressively faster (Δvelocity, $p = 0.01$), maintaining high resistive force, even as error-dependent penalties decreased.
Learning was unexpectedly indifferent to moderate effort incentives or deterrents despite the lack of reward, and, in the error-congruent group maintained resistive force by moving faster. These findings lead to further questions about how the brain senses and weighs effort in adaptive motor control and how changes in effort influence subsequent movement selection.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

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Program #/Poster #: PSTR062.12/DD14

Topic: F.04. Voluntary Movements

Support: JST/PRESTO:JPMJPR23S8
JSPS KAKENHI: JP23H03296

Title: A quaternion-based framework geometrically distinguishes between task-space alignment and within-space adjustments in de novo motor learning

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Abstract: Acquiring a novel skill ("de novo" learning) requires constructing a new visuomotor mapping (Krakauer et al., 2019) while motor adaptation recalibrates existing visuomotor

mappings (Hayashi et al., 2016). These processes involve both identifying a task-relevant space and refining visuomotor mappings within it, respectively. However, it remains unclear how the central nervous system (CNS) coordinates these processes largely due to the absence of a framework to quantitatively assess them. Geometrically, these processes correspond to aligning the movement manifold with the task space and adjusting the manifold within the space. To distinguish between task-space alignment and within-space adjustments, we introduced a quaternion-based framework that geometrically decomposes movement manifold organization into "Swing" (task-space alignment) and "Twist" (within-space adjustments).To investigate de novo formation of a visuomotor map with a quaternion-based framework, 30 participants (12 females, mean ± s.d. age 31.4 ± 11.1 years) performed a sequential target acquisition task, in which participants were required to use a 2D cursor controlled by high-dimensional hand gestures to hit as many targets as possible per 2-minute block. They completed a baseline phase (16 blocks) followed by a mirror reversal phase (12 blocks) inverting an axis (Kasuga et al., 2015). A mirror reversal is a unique geometric perturbation: it cannot be resolved by within-space adjustments (Twist); rather, it requires flipping the manifold's polarity, a task-space realignment (Swing).The number of target acquisitions significantly increased during baseline but was markedly suppressed by the mirror reversal. Crucially, our quaternion analysis revealed distinct dynamics for the two geometric components. During baseline, the Swing error gradually decreased as the movement manifold aligned with the task space. Upon mirror reversal, the Swing update revealed manifold polarity flipping to accommodate the inverted mapping, while the Twist error remained near zero across all experimental phases. These results suggest that our Swing and Twist indices can capture not only task-space alignment, a key feature of de novo motor learning, but also the manifold realignment required for mirror reversal, while effectively dissociating these processes from within-space adjustments. This quaternion-based framework thus provides a novel computational perspective on how the CNS efficiently resolves high-dimensional de novo motor learning.

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Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

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Topic: F.04. Voluntary Movements

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Stratton Veterans Affairs Medical Center

Title: Heksors in negotiation - normal locomotion and bidirectional locomotion: initial analyses

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Abstract: Recognition that the CNS is plastic through life requires a new paradigm to explain how skills are acquired and maintained. The paradigm's core is a newly recognized CNS entity, now called a "heksor" from the ancient Greek "hexis" (JPhysiol 2022 DOI:10.1113/JP283291). A heksor produces a skilled behavior (e.g., locomotion). It is a distributed network of neurons and synapses that may extend from cortex to spinal cord. A heksor has two unique properties. First, it changes itself as needed to maintain the key features of its skill, the attributes that make the skill satisfactory. The CNS activity, muscle activity, and kinematics of locomotion may change, but key features (e.g., upright posture, good balance, right/left symmetry, acceptable metabolic cost) are maintained. Second, through their concurrent changes, the many heksors that share the CNS negotiate the properties of the neurons and synapses they all use. Heksors keep the CNS in a negotiated equilibrium that enables each to maintain its skill. We are studying negotiation of the equilibrium between the heksor of normal treadmill locomotion (NTL) and the new heksor created by practicing bidirectional treadmill locomotion (BDTL). We hypothesize that BDTL training will change NTL EMG and kinematics but will not impair its key features. Each of 6 healthy adults completed 24 sessions (3/wk). In a session, the person first walked for 2 min on a Bertec split-belt treadmill with both belts at 80% of their preferred speed. They then walk for four 5-min training blocks with left(L)-belt movement the same as baseline and right(R)-belt movement at equal speed in the opposite direction. Lastly, they again walked with both belts in the same direction. We recorded ground reaction forces; center-of-pressure; & EMG activity from tibialis anterior (TA), soleus, rectus femoris & biceps femoris bilaterally. Before, during, & after the sessions, we recorded locomotor kinematics; and we elicited in both legs: motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS); TA & soleus H-reflex recruitment curves; and sensory evoked potentials (SEPs) to vibrotactile & electrical stimulation to the foot sole & the tibial nerve, respectively. Initial analysis shows for NTL a decrease in left step length and an increase in step length asymmetry ($p = 0.005$ & 0.043, respectively). Asymmetry does not exceed the range seen before BDTL training. NTL is not impaired, but it is affected by BDTL training. In contrast, BDTL temporal features (double-stance, R stance/L swing, 2nd double-stance, R swing/L stance) change significantly over training. We are going on to analyze the effects of BDTL training at spinal and supraspinal levels.

Disclosures: J.R. Wolpaw: None. **R.L. Hardesty:** None. **H. Mojtabavi:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.14/DD16

Topic: F.04. Voluntary Movements

Support: DST CSRI(DST/CSRI/2021/164(C)(G))

Title: Effect of Training Schedule on Consolidation and Savings of Competing Motor Memories

Authors: *V. KHARE[1], N. KUMAR[2];
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Abstract: Context-dependent motor learning requires the brain to form, segregate, and selectively retrieve multiple competing motor memories. Although contextual signals are known to divide motor adaptation into discrete representations, it is not yet known how the temporal organisation of training influences their consolidation after 24 hours and future relearning. We investigated whether random, sequential, and gradual dual-context visuomotor training schedules differentially affect memory segregation at acquisition, consolidation, and savings during relearning, and whether evoked trials from one specific context selectively bias consolidation. Ninety healthy adults (n=15/group) adapted to opposing visuomotor rotations (+/-30 degrees), each paired with a distinct spatial context cue, under one of three training structures (random interleaved, sequential blocked, or gradual blocked), with or without evoke trials immediately after learning to probe selective memory consolidation. Following consolidation, participants completed retention trials under one contextual cue, then a full relearning session identical to Day 1. All six groups achieved robust within-session adaptation. Overnight retention was observed exclusively in sequential groups. Random and gradual groups showed near-zero retention. However, significant savings were noted across all abrupt groups, with random interleaving showing the most substantial effects, leading to a clear distinction between overnight expression and reacquisition through relearning. The savings were indicated by higher starting intercepts on Day 2, without significant differences in the relearning slope, consistent with the rapid re-emergence of latent memory traces. Gradual training did not support retention or detectable savings, further proving that the magnitude of the error signal is essential for encoding that supports consolidation. End-of-day evocation enhanced retrieval under random schedules but appeared ineffective under sequential conditions, challenging uniform reactivation-based accounts of selective consolidation. Overall, our findings suggest that training structure influences which memory processes are engaged, and that immediate retrievability, consolidation, and savings are dissociable features of dual-context motor memory.

Disclosures: V. Khare: None. **N. Kumar:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.15/Web Only

Topic: F.04. Voluntary Movements

Support: Prime Minister's Research Fellowship, Govt. of India

Title: Error Controllability Determines Attenuation of Implicit Sensorimotor Relearning

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Abstract: Adaptive behavior depends not only on learning from errors, but also on regulating how strongly those errors drive future learning (Albert et al., 2021; Herzfeld et al., 2014). Consistent with this idea, we recently demonstrated that repeated exposure to sensory prediction errors (SPEs) generated via error clamps leads to attenuation of implicit learning, reflecting a history-dependent reduction in error sensitivity (Sahu & Mutha, 2026). Why does repeated exposure to error clamps reduce error sensitivity? We hypothesize that the reduction in sensitivity underlying attenuation arises from repeatedly experiencing errors that cannot be reduced through learning. Accordingly, if errors remain behaviorally reducible, attenuation should be absent. To test this idea, we examined attenuation in a visuomotor rotation (VMR) adaptation paradigm that isolates SPE-driven learning but minimizes task performance errors and strategic corrections. Participants adapted to a VMR while reaching to an arc-shaped target in which cursor deviation generated SPEs but curtailed strategy use (Shingane et al., 2025). Implicit adaptation was quantified using interleaved no-feedback catch trials. Preliminary analyses revealed no evidence of attenuation during re-learning, consistent with the hypothesis that attenuation depends on exposure to irreducible SPEs. To further test this hypothesis, we are conducting two additional experiments in which SPEs remain reducible. In one experiment, learning is driven primarily by SPEs by jumping a point target onto the rotated cursor during adaptation, thereby eliminating performance errors (Leow et al., 2018). In the second experiment, participants are instructed to ignore the VMR altogether (Morehead et al., 2017). Together, these experiments will determine whether attenuation is a general consequence of repeated SPE exposure or instead depends on the irreducibility of experienced errors. More broadly, these findings will test whether learning systems regulate error sensitivity according to the controllability of prediction errors.

Disclosures: A. Sahu: None. **P.K. Mutha:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.16/Web Only

Topic: F.04. Voluntary Movements

Title: An explicit strategy overrides implicit recalibration during adaptation to movement extent

Authors: *P. GUPTA, P. K. MUTHA;
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Abstract: A dominant idea in human motor learning is that sensory prediction errors trigger implicit recalibration of sensorimotor mappings that is uninfluenced by task success and volitional intent. This understanding is based primarily on visuomotor rotation learning

paradigms, in which the rotated visual feedback produces systematic direction errors. Prevailing theories assume that prediction errors engage a common implicit mechanism that operates similarly across different perturbations. Accordingly, any prediction error should elicit an implicit response that is resistant to explicit instruction. However, this cannot be adequately tested using rotation paradigms because direction errors inherently require structural or geometric remapping of the hand-feedback relationship. As a result, error is confounded with the need to modify the mapping structure. Visuomotor gain perturbations however can fill this critical gap. Gain perturbations scale the relationship between hand movement and its feedback, producing errors in movement extent while preserving directional structure. Because these errors can be resolved through parametric adjustment without altering mapping geometry, gain perturbations dissociate the presence of error from the requirement for structural reorganization. We tested whether explicit strategies can fully compensate for such perturbations and prevent implicit adaptation. Participants performed out-and-back movements under an additive translation of the hand-feedback mapping. One group was provided an explicit strategy to counter the perturbation, while a second group adapted without instruction; a control group executed the same strategy without perturbation. Implicit learning was assessed via post-adaptation aftereffects. Strategy participants rapidly eliminated the perturbation and did not show aftereffects, indicating minimal implicit adaptation. In contrast, the adaptation group showed gradual error reduction and robust aftereffects, consistent with implicit recalibration. The control group showed no aftereffects, confirming that strategy use alone does not induce adaptation. Ongoing work tests whether this pattern generalizes to multiplicative gain perturbations. These results suggest that implicit adaptation is not obligatorily engaged by all prediction errors but depends on perturbation structure, specifically whether errors require structural reorganization or can be resolved through parametric adjustment.

Disclosures: P. Gupta: None. **P.K. Mutha:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.17/Web Only

Topic: F.04. Voluntary Movements

Title: Frontal-Motor Connectivity During Interlimb Generalization of Motor Skill Varies with Practice Duration: An EEG Study

Authors: *R. PAL[1], G. YADAV[2], N. KUMAR[1];
[1]Indian Inst. of Technol. Hyderabad, Sangareddy, India; [2]Univ. catholique de Louvain, Brussels, Belgium

Abstract: Interlimb generalization is a prominent feature of motor skill acquisition, where practice with one limb leads to performance improvements in the opposite, untrained limb. Our prior work demonstrated that interlimb generalization was impaired when a cognitively

demanding secondary task was introduced following short, but not long, skill training. However, the neural mechanisms underlying interlimb generalization particularly the role of practice duration (short vs. long training) remain poorly understood. To investigate this, we recruited 20 right-handed healthy adults. Participants underwent either short- or long-duration training on a motor skill task with their right hand, and generalization to the left hand was assessed 24 hours later. EEG was recorded during both the training and generalization sessions, and resting-state EEG was additionally recorded for five minutes before and after each learning session. Both groups demonstrated interlimb generalization, however, the extent of generalization was significantly reduced in the short-training group relative to the long-training group. A preliminary analysis of beta oscillatory dynamics and functional connectivity was then conducted. Using phase-based Phase Locking Value (PLV) connectivity analysis, we focused on two regions of interest: the primary motor cortex (M1, C3 electrode), and the dorsolateral prefrontal cortex (DLPFC, F3 electrode). Beta power was desynchronized during movement and resynchronized following movement offset, with comparable magnitudes between the short- and long-training groups. Critically, frontal-to-motor (F3-C3) PLV connectivity was significantly higher in the short-training group during the interlimb generalization session relative to the long-training group. This suggests that motor memory had not been fully stabilized following short training, and that participants consequently relied more heavily on the DLPFC during generalization. In contrast, the long-training group exhibited lower frontal-motor phase-locking during generalization, consistent with a more consolidated and efficient motor representation that required less top-down cognitive support.

Disclosures: R. Pal: None. **G. Yadav:** None. **N. Kumar:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.18/DD17

Topic: F.04. Voluntary Movements

Support: NIH R35 NS122266

Title: Unsupervised Behavioral Clustering Reveals Age-Dependent Motor Strategies During Reinforcement Locomotor Learning

Authors: *N. CASTLE[1], A. J. BASTIAN[2,3];
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Abstract: During locomotor learning, many different stepping patterns may be explored to find one that best accounts for new situations. Consider a child learning to walk in rain boots: they will move their legs in different ways until they find a pattern that leads to stable footing. We previously showed that there is a developmental time course of reinforcement locomotor

learning: younger children demonstrate less successful stepping patterns than older children. We also showed that younger children fail to differentiate their stride adjustments after successful versus failed attempts, while older adolescents show mature explore-exploit behavior. However, traditional summary metrics like success rate alone may obscure qualitatively different strategies that children use to approach the task. Here, we applied unsupervised behavioral clustering to stride-level kinematic data to discover distinct motor strategies and ask whether they differ across development.
Children (N=53, ages 7-18) walked on a treadmill and adjusted their stride length in response to binary reinforcement feedback. We calculated traditional summary metrics like success rate and extracted interpretable features from each stride, including step lengths, percentage of the gait cycle in stance and swing, double support times, lateral foot excursion, and gait asymmetry. We applied a dimensionality reduction algorithm called UMAP followed by a spatial clustering algorithm called HDBSCAN to identify distinct behavioral patterns.
We identified distinct behavioral clusters that varied substantially in both spatial and timing features. Biomechanical timing features, particularly double support duration, dominated cluster discrimination. Some clusters were characterized by longer double support times and shorter strides, reflecting a cautious, stability-prioritizing pattern, while others showed shorter double support and longer strides, consistent with more dynamic walking. Several behaviors showed significant relationships with age. These results suggest that younger and older children solve the same reinforcement learning task using qualitatively different motor strategies, and that developmental changes in strategy selection, not just overall performance, shape the trajectory of locomotor learning.

Disclosures: N. Castle: None. **A.J. Bastian:** None.

Poster

PSTR062: Motor Learning: Human (Behavior/Physiology/Imaging) I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR062.19/DD18

Topic: F.04. Voluntary Movements

Title: Role of Somatosensory Cortex in the Consolidation of Implicit Motor Memory Acquired through Compound Learning

Authors: *A. D. KUMAR[1], A. K. VERMA[2], N. KUMAR[1];
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Abstract: Motor adaptation recruits both implicit recalibration and explicit strategic processes. When probed immediately after learning, these processes are expressed as a unified motor behaviour, but separate into independently retrievable components following offline consolidation. The somatosensory cortex has been implicated in motor memory consolidation, predominantly in implicit learning. However, existing evidence derives from learning perturbations that engage these processes in isolation, and the role of S1 in the consolidation of

compound learning remains unresolved. Here, we applied continuous theta-burst stimulation (cTBS) immediately following a compound visuomotor adaptation task consisting of simultaneous target-jump (explicit) and gradual cursor rotation (implicit) perturbations. Healthy participants (N = 36) were assigned to one of three stimulation groups targeting somatosensory cortex, primary motor cortex, or sham stimulation. Retention of the implicit component was assessed 24 hours later using zero-error-clamp trials. All groups acquired comparable levels of adaptation and exhibited similar implicit aftereffects during learning and equivalent acquisition of the compound memory. However, retention differed significantly across stimulation conditions. Participants who received cTBS over S1 showed substantially reduced retention compared with both the M1 and sham groups. In contrast, retention following M1 stimulation was indistinguishable from sham stimulation. These findings extend previous evidence and demonstrate that stabilization of implicit motor memories formed during compound learning might also depend on the somatosensory cortex.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.01/DD19

Topic: F.05. Brain-Machine Interface

Support: NIH Grant F32MH139145-01
NIH Grant UH3 NS107714

Title: Reshaping cortical motor circuits using an intracortical brain-computer interface

Authors: *H. R. SCHONE[1], B. DEKLEVA[2], C. M. GREENSPON[4], J. E. DOWNEY[5], A. P. BATISTA[3], J. L. COLLINGER[2];
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Abstract: Intracortical brain-computer interfaces (iBCIs) enable individuals with paralysis to control external devices by decoding movement-related neural activity from the precentral gyrus. Classical models of this region propose a somatotopic organization in which body parts occupy distinct cortical territories, suggesting implant location constrains which body parts can be decoded. This introduces a real practical challenge when implanting iBCI electrodes, as neurosurgical access to desirable territories is often limited by specific clinical conditions (e.g., stroke), minimal electrode coverage, and expansive neurovascular anatomy. These limitations raise two central questions: how much whole-body movement information is accessible from any given precentral gyral region, and can iBCI use be leveraged to modify local cortical motor representations at the implant site to better support desired BCI functions? We studied two individuals with a cervical spinal cord injury implanted with microelectrode arrays in the hand

region of the precentral gyrus as part of an iBCI clinical trial (NCT1894802). Using a whole-body motor mapping task involving directional movements of 12 body parts, we observed significant neural modulation for all tested movements. Results were consistent with a graded somatotopic hierarchy: hand responses were strongest, while leg and face responses were weaker, but significantly detectable. We next tested whether these latent representations could be strengthened through targeted iBCI training. One participant completed five sessions controlling a BCI using neural activity generated from attempting to move the weakly represented ankle. Across sessions and all tasks, BCI performance improved significantly with training. In parallel, neural separability of ankle movements increased from 57% to 90% (5-class decoding), whereas wrist representations remained relatively stable (92% to 96%), suggesting selective strengthening of the ankle representation. Finally, we initiated a longitudinal study to determine whether routine motor iBCI use similarly alters native cortical representations. One participant underwent monthly motor mapping assessments post-implant. Over one year, across 53 testing sessions, the participant completed 98 hours of experimental testing, including 22 hours of online motor iBCI control. Ongoing analyses are evaluating effects of BCI usage on cortical organization. Together, these findings suggest that latent motor representations are broadly accessible across the precentral gyrus and that targeted iBCI training may provide a mechanism for selectively reshaping cortical motor circuits.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.02/DD20

Topic: F.05. Brain-Machine Interface

Support: Chalmers Area of Advance Health Engineering 2026
NIH R35 NS122333
NIH UH3NS107714

Title: Population encoding of co-speech gestures in human motor cortex

Authors: S.-S. GORRIZ[1], Y. WON[2], M. CATTABRIGA[1], M. NIELSEN[2], L. F. SCHIFFL[4], J. E. DOWNEY[3], S. N. JACOB[5], *G. VALLE[1];
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Abstract: Paralysis can strip individuals of their ability to physically and verbally interact with their environment, severely limiting communication. Brain-computer interface(BCI) research on upper-limb restoration has focused on goal-directed actions (e.g., reaching and grasping), leaving

communicative actions unexplored. Yet gestures are fundamental to human communication, conveying semantic, spatial and emotional information that complements speech, facilitating interpersonal interaction. Despite their importance, it is unclear how language-related processes interact with motor cortical activity to generate gestures coordinated with speech. This is especially relevant for BCIs, which often rely on signals from the hand knob region of the motor cortex (MC), an area potentially involved in speech-accompanying gestures. We recorded hand knob MC (BA4 and 6d) activity via Neuroport Electrodes from two paralyzed participants. In a first task covering dexterous gestures and speech, stable event-locked neural responses were observed across speech-only, co-speech gestures, and gesture-only conditions. Electrode modulation and low-dimensional population trajectories revealed behavior-specific neural signatures, showing that speech and gesture engage distinct motor cortical representations. Concurrent speech enhanced rather than attenuated representational discriminability, resulting in higher decoding accuracy for co-speech gestures, indicating facilitatory speech-gesture coupling. Additionally, inhibitory modulation during movement preparation in speech-only trials suggested suppression of hand-related motor activity. A second task examined whether speech semantics influence gesture representations using congruent and incongruent co-speech gestures. No systematic congruency effect was found, suggesting that semantic processing does not directly modulate MC activity. However, congruent co-speech gestures yielded the most separable movement representations, suggesting semantically matched speech stabilizes motor cortical representations. These results support the hypothesis that broad, overlapping somatotopic MC maps facilitate coordinated movements, likely not as an exclusive hand-mouth link, but as part of a broader bodily coordination mechanism. Together, these findings suggest motor BCIs may extend to communicative contexts, potentially offering individuals with tetraplegia an additional means of interaction through restored multimodal communication. Data were collected as part of a clinical trial conducted under an FDA Investigational Device Exemption(NCT01894802).

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

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Program #/Poster #: PSTR063.03/DD21

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS 1R01NS130302

Title: Speed decoding in an implanted brain-computer interface improves coordinated movements of a virtual robotic arm

Authors: *M. M. ISKAROUS[1], J. YE[3], Y. WON[1], L. E. MILLER[4], J. L. COLLINGER[5], N. G. HATSOPOULOS[2], J. E. DOWNEY[1];
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Abstract: Natural reaching entails the coordinated movements of joints distributed over the entire upper limb - including the arm and hand. Despite this, brain-computer interface (BCI) decoders for restoring upper limb movement have been trained with isolated, sequential movements of the arm, wrist, and hand. These decoders often do not generate smooth, quick movements seen in native arm use during tasks requiring coordinated movements. Additionally, previous work in non-human primates has demonstrated tuning to movement speed in addition to velocity, as well as shifts in tuning with increasing movement complexity. Here we show that including a normalizing speed term in a decoder trained on data from a task requiring coordinated movements improves BCI control. Data was collected from 3 participants (C1, C2, and P4) each implanted with two NeuroPort Electrode arrays in motor cortex (192 electrodes total, Blackrock Neurotech) as part of an ongoing clinical trial conducted under an FDA Investigational Device Exemption (NCT01894802). Each participant completed a robot arm control task in virtual reality that required coordination of at least 4 degrees of freedom (DoFs) across at least 2 of the 3 upper limb movement domains (arm, wrist, and hand). The task was completed using two motor decoders: a traditional velocity-based (V) decoder (based on indirect optimal linear estimation) and a new version that added a speed term with normalization across DoFs (V+S). The participant failed a trial if any phase of the task timed out (> 10 s) before they achieved the target posture in all DoFs. Computer assistance was titrated until the user had unassisted control of the arm. Performance metrics were computed for the unassisted trials. As a group, the participants completed 470 trials with each decoder. They succeeded on 189 and 269 trials with V and V+S decoders, respectively (2-tailed 2-proportion z-test: $p = 1.79e-7$; Cohen's h: $h = 0.342$). This initial result is promising evidence for the benefit of adding a speed term to the decoder when completing coordinated tasks. Further analysis will be done on this dataset focusing on the kinematic performance of the decoder: trial completion time, path efficiency, tune-in, and coordination. This important addition to decoder design promises to improve the smoothness and naturalness of BCI-controlled prosthetic arms for activities of daily living.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

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Program #/Poster #: PSTR063.04/DD22

Topic: F.05. Brain-Machine Interface

Support: NIH UH3NS107714
NIH R35 NS122333
Chalmers Area of Advance Health Engineering 2026
ECS 00000017

Title: Gaze-related neural dynamics in the human motor cortex during target-directed reaching

Authors: *M. ULIANO[1,4], Y. WON[5], M. CATTABRIGA[2], M. NIELSEN[5], J. E. DOWNEY[6], M. CONTROZZI[4], G. VALLE[3];
[2]Chalmers Univ. of Technol., [3]Dept. of Electrical Engin., [1]Chalmers Univ. of Technol., Gothenburg, Sweden; [4]The Biorobotics Instiute, Scuola Superiore Sant'Anna, Pontedera, Italy; [6]Dept. of Neurolog. Surgery, [5]Univ. of Chicago, Chicago, IL

Abstract: Intracortical brain-computer interfaces (iBCI) typically rely on neural activity recorded from the premotor and motor cortex (MC) to decode movement intention and control external devices. However, voluntary actions emerge from sensorimotor processes involving multiple brain regions responsible for movement planning and sensory integration, including gaze coordination. While the encoding of visually guided target-reach movements have been extensively studied in non-human primate MC, it remains unclear to what extent visual information is integrated with motor representations in human MC. Although compositional coding of visual and motor variables has been demonstrated in posterior parietal cortex, most iBCI systems rely predominantly on MC activity, where visuomotor encoding principles are still incompletely characterized. To this aim, we simultaneously recorded gaze and MC activity from participants implanted with NeuroPort Electrodes during a center-out task. We tested 4 conditions: *free-gaze* (no gaze restrictions); *gaze-on-center* (central fixation during movement); *gaze-on-target* (target fixation during movement); and *gaze-only* (target-directed gaze shift without movement). The neural dynamics of target-reach movements were largely preserved across gaze conditions. Target decoding accuracy remained above chance across movement conditions, and neural dynamics showed consistent trajectories regardless of gaze behavior. Despite preserved motor representation, gaze modulated the magnitude of multi-unit movement-related responses at the single-electrode level. For a given target direction, the *gaze-on-target* condition elicited stronger neural responses than the *gaze-on-center* condition. In contrast, *gaze-only* trials did not evoke robust direction-selective response, indicating minimal oculomotor response in the hand knob. However, a subset of electrodes showed inhibitory modulation temporally locked to gaze-shift onset, potentially reflecting suppression of movement-related activity rather than gaze processing. These results reveal only partial gaze modulation of MC activity, suggesting complementary contributions of MC and gaze signals to motor decoding. Building on these findings, we designed hybrid motor decoders integrating MC activity and gaze signals during a center-out task. Preliminary results improved target classification and cursor velocity prediction compared with neural-only decoders, supporting multimodal motor decoding as a promising approach to improve iBCI. Data were collected as part of a clinical trial conducted under an FDA Investigational Device Exemption(NCT01894802)

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant 5R01NS121079-05

Title: Impact of fatigue on human motor cortex activity

Authors: *N. G. KUNIGK[1,2,8], W. HOCKEIMER[2,3], A. ALREJA[4], R. J. SOLINSKY[9,10], L. M. BYLSMA[5,6], J. MAYO[7,1], S. M. CHASE[11,8,12], M. L. BONINGER[3,1,2], B. M. DEKLEVA[3,2,8], J. L. COLLINGER[3,1,2,8,12];
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Abstract: Despite advances in decoding algorithms, intracortical brain-computer interfaces (iBCIs) can experience large fluctuations in day-to-day performance. Work in nonhuman primates has implied that factors such as internal state can affect the motor cortex activity that iBCIs use to provide control. Increases in states such as fatigue may negatively affect iBCI performance. Since even decoding algorithms trained on new data (minimizing neural drift effects) can experience high performance variability in humans, we hypothesize that fatigue may reduce the quality of daily calibration data and subsequent online performance.
Here, we investigated the impact of fatigue on human motor cortex activity in a participant with tetraplegia enrolled in an ongoing clinical trial of an iBCI conducted under an FDA Investigational Device Exemption (NCT#01894802). The participant had two NeuroPort Electrode arrays (100 electrodes each, Blackrock Neurotech) implanted in motor cortex. Biometric data were recorded using eyetracking glasses (Pupil Labs) and a biometric ring to monitor heart rate (BIOPAC Systems, Inc) while the participant performed a 2D cursor center-out iBCI task. Experiments consisted of two types of trials: (1) in open-loop calibration sets, the participant watched the computer perform the task while following along with motor imagery; (2) in closed-loop sets, the participant was given control of the cursor via an iBCI decoder trained with neural data from the open-loop set. Biometric indications of fatigue in open-loop sets were correlated with task completion times in the closed-loop sets trained on their neural data. Specifically, biometrics positively associated with fatigue had a negative correlation with completion time (blink rate = -0.47, $p < 0.0005$; LF/HF ratio, a measure of heart rate variability: $r = -0.58$, $p < 0.05$). Conversely, mean eyelid aperture (negatively associated with fatigue) showed a positive correlation with completion time ($r = 0.40$, $p < 0.005$. All metrics $n = 58$ sets) Furthermore, open-loop sets in which the participant displayed higher indices of fatigue (above average blink rate and below average mean eyelid aperture) had significantly lower firing rates (mean firing rate across all electrodes and sets: 6.23 ± 1.66 Hz high fatigue vs 12.87 ± 2.80 Hz low fatigue, $t = -6.12$, $p < 1e\text{-}8$, ind. samp. t-test, $n = 16$ sets both groups), providing a potential explanation for the decrease in iBCI performance.
These preliminary single-participant results indicate that user fatigue can change human motor cortex activity and may influence iBCI control, implying a potential avenue for the improvement of these systems by accounting for user mental state.

Disclosures: N.G. Kunigk: None. **W. Hockeimer:** None. **A. Alreja:** None. **R.J. Solinsky:** None. **L.M. Bylsma:** None. **J. Mayo:** None. **S.M. Chase:** None. **M.L. Boninger:** None. **B.M. Dekleva:** None. **J.L. Collinger:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.06/DD24

Topic: F.05. Brain-Machine Interface

Support: 5R01NS125270-05
R01 NS131953
PAR-24-128

Title: Modulation of ipsilateral hand representations in human motor cortex

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Abstract: Humans execute hand movements with finesse - from the independent rhythms of a harpist to the coordinated gestures of sign language - whether acting unilaterally or across both hands simultaneously. Bimanual performance is sensitive to hand symmetry, with incongruent movements producing greater interference and poorer task execution. This capacity for flexible hand coordination across unimanual, symmetric, and asymmetric bimanual tasks is primarily driven by contralateral motor cortex (MC), yet a relevant ipsilateral representation co-exists within the same hemisphere. Non-invasive human imaging studies have established that ipsilateral MC activity is also modulated by unimanual and bimanual finger movements. How these signals encode explicit hand movements and postures at the single unit level, however, has yet to be directly investigated. To address this question, we recorded multi-unit activity from chronically implanted NeuroPort microelectrode arrays in the left precentral gyrus of two right-handed human BCI participants (Clinical trial NCT01894802) during imagined digit and wrist movements across unimanual, bimanual, and asymmetric bimanual contexts. To characterize baseline ipsilateral hand representations, digit identity was decoded from MC separately during ipsilateral and bimanual movements using a linear classifier. Ipsilateral digit identity was decodable above chance in both contexts, with classification accuracy rising from command presentation through movement start, confirming a temporally structured, decodable ipsilateral representation coexists with dominant contralateral signals in human MC. To determine whether symmetry between hand segments across the upperlimb modulates ipsilateral representational stability, we compared congruent bimanual pairings - matched digit movements across both hands - to incongruent pairings, in which digit movements on one hand were paired with simultaneous wrist movement on the other. During congruent bimanual pairings, contralateral

and ipsilateral classification accuracy remained above chance as demonstrated in previous experiments. Incongruency did not strongly affect the classification accuracy of ipsilateral digits, yet contralateral digit representations became weaker during this trial type. These results provide human single-unit evidence that ipsilateral MC encodes hand movements in a unique context- and effector-dependent manner, with direct implications for bimanual brain machine interface design, post-stroke rehabilitation, and dexterous hand control.

Disclosures: K. Adegebsan: None. **A.R. Sobinov:** None. **N.G. Hatsopoulos:** None. **A.M. Emonds:** None. **S.E. Palmer:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

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Program #/Poster #: PSTR063.07/DD25

Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1R01NS123663-01

Title: Resolving the functional organization and neural basis of visuomotor planning in posterior parietal cortex with functional ultrasound and electrophysiology

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Abstract: The posterior parietal cortex (PPC) receives visual information about the external world and transforms it into plans for action, yet we still do not understand how this association cortex organizes and processes the many visual, motor, and cognitive variables that guide behavior. Functional ultrasound (fUS) offers a way to study this organization at the mesoscale, combining wide field of view, high spatial resolution, and stable signals over time. We previously showed that fUS can resolve the functional organization of planned saccade direction in macaque lateral intraparietal area (LIP), and more recently found that PPC activity is modulated by action context and internal state. In a value-modulated saccade task, expected reward produced broad changes in PPC activity, while both saccade direction and reward value could be decoded from the same imaging plane. Direction decoding was stronger on high-value trials, suggesting that motivational state changes the population activity patterns supporting visuomotor planning. During the preparatory period of the task, before target location was available, PPC exhibited widespread suppression with smaller regions of increased activity. This preparatory activity showed distinct spatial patterns before saccade versus reach trials and greater relative activation in high-value contexts, indicating that PPC enters a task- and value-dependent state before visual information is transformed into an action plan. Parallel electrophysiological recordings revealed corresponding changes in spiking activity and local field potentials,

providing candidate neural correlates of these hemodynamic signals. Together, these results show that fUS can map spatially organized visual, motor, and motivational signals across macaque PPC. By revealing how planned actions and internal states can be read out from hemodynamic activity, this work motivates continued development of fUS-based brain-machine interfaces for minimally invasive access to cognitive and motor variables in association cortex.

Disclosures: T. Callier: None. **L. She:** None. **W.S. Griggs:** None. **T. Deffieux:** None. **C. Liu:** None. **M. Tanter:** None. **M.G. Shapiro:** None. **R.A. Andersen:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.08/DD26

Topic: F.05. Brain-Machine Interface

Support: FWO Postdoctoral Fellowship Junior 1264926N
UG1EY032039
Tianqiao and Chrissy Chen Brain-Machine Interface Center
Boswell Foundation

Title: A Shared Neural Substrate for Actions and Intuitive Physics in Human Posterior Parietal Cortex

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Abstract: To interact successfully within a dynamic environment, the brain must have an internal model of the environment and the relation of the body to that environment. Extensive research has focused on the role of posterior parietal cortex (PPC) in visually guided action planning and in action observation. Interestingly, similar cortical regions appear active when viewing physical interactions of objects, suggesting that the internal model extends beyond the direct interaction of the body with the world. Here, we recorded single unit activity (SUA) and local field potentials (LFPs) from two individuals (JJ, RD) with spinal cord injury implanted with a total of three Utah arrays in PPC (two in superior parietal lobule (SPL) and one in supramarginal gyrus (SMG)) to test whether intuitive physics and action processing rely on overlapping neural representations. We recorded from more than 2000 units while participants performed two intuitive physics paradigms: a tower stability judgment task with a color judgment control condition, and passive viewing of naturalistic videos depicting physical versus social events. We provide the first single neuron evidence implicating human PPC in intuitive physical reasoning. SPL units exhibited selective responses for physics across both experiments,

with many of the same units retaining their selectivity across the two tasks, suggesting abstract representations of physics that generalize across contexts. In contrast, SMG responses were largely restricted to the tower stability judgment task and emerged later in time, suggesting a higher-level contribution to goal-driven physical inference. None of these effects could be explained by general task difficulty suggesting a distinction from the domain-general multiple demand network. We next asked whether these neural representations overlap with those involved in action processing. In participant RD, we directly compared neural responses across the physics tasks and action intention and observation paradigms recorded from the same PPC populations. During the action tasks, RD either observed videos of hand object interactions involving object pulling or object contact or intended the same actions. Notably, SPL populations activated during physical reasoning also tended to be activated during action tasks, whereas no such relationships were observed for perceptual control conditions or passive viewing of social events. These findings suggest that intending and perceiving actions and intuitive physics rely on partially shared representations within SPL, supporting the idea that this region may construct internal models of both the body and the surrounding environment.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.09/DD27

Topic: F.05. Brain-Machine Interface

Support: NIH Grant F30 NS145610
Tianqiao and Chrissy Chen BMI Center
Merkin Institute for Translational Research

Title: Functional ultrasound imaging through a human cranial window for mesoscopic mapping of motor effector encoding within the sensorimotor cortex

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Abstract: Understanding movement encoding within human cortical circuits has been essential for advancing brain computer interfaces (BCIs). However, there are limited minimally invasive, high resolution neurorecording methods sensitive enough to detect single-trial movement-correlated neural activity. Electrophysiological methods require highly invasive brain surgery for electrode implantation while conventional non-invasive imaging techniques like fMRI and EEG

lack sufficient spatial resolution for high-bandwidth BCI use. Functional ultrasound imaging (fUSI) provides submillimeter spatial resolution of deep cortical tissue with high sensitivity and, when paired with acoustically transparent skull implants, enables transcutaneous recording of human neurovascular changes. Prior studies have used fUSI in participants with acoustically transparent skull implants for on-off task mapping and decoding. In this study, we demonstrate fUSI's ability to reliably resolve multi-body-part and single digit movement encoding within the primary sensorimotor cortex in a participant with an acoustically transparent skull implant.
Experiments were performed on a human participant who had previously undergone a hemicraniectomy procedure and polymeric skull reconstruction including an acoustic window. The participant was asked to perform randomized instructed movement tasks in a blocked design using different body parts or "effectors" - multi-body-part (wrist, finger, lip, tongue) and single digit (thumb, index, middle, ring, pinkie fingers) - while we acquired fUSI data from a fUSI plane containing the left sensorimotor cortex and the supramarginal gyrus.
Using fUSI, we obtained fine-grained mappings of individual effector representation that were consistent with classic somatotopy for both multi-body-part and single digit movement. We were able to resolve single-trial event-related activity, enabling single-trial decoding of both conditions. Analysis of voxels important for decoding suggested differential encoding of single digit movement information across the different Brodmann areas. Finally, we show that these patterns of representation can be approximated across sessions recorded on different days, allowing for cross session decoding.
These results establish that fUSI can reliably delineate somatotopically organized motor representations at submillimeter resolution, bridging a critical gap between invasive electrophysiology and noninvasive hemodynamic imaging in a human subject. This highlights the potential of fUSI as a minimally invasive alternative for BMIs in the future.

Disclosures: L.J. Lin: None. **T. Callier:** None. **K. Pejsa:** None. **C. Liu:** None. **M.G. Shapiro:** None. **R.A. Andersen:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.10/DD28

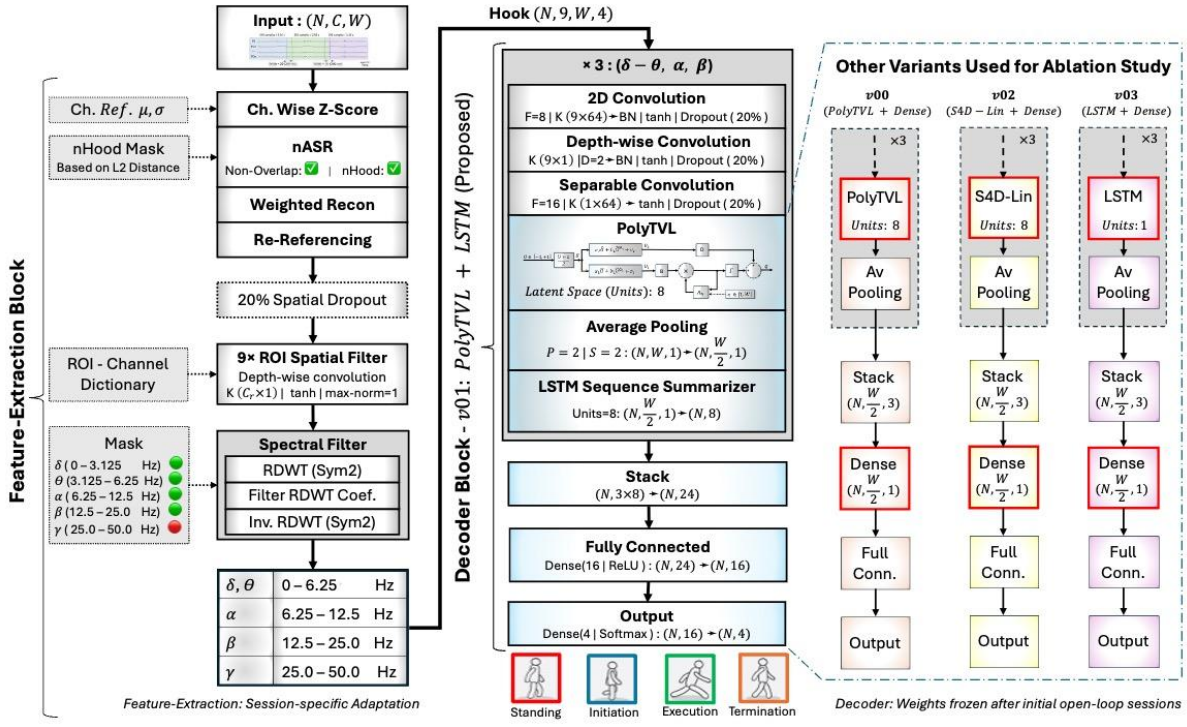
Topic: F.05. Brain-Machine Interface

Support: NSF IUCRC BRAIN 2137255

Title: Real-Time EEG-Based Four-State Gait Decoding via a Modular 2-Block BCI Architecture: A Closed-Loop Pilot Study

Authors: *S. SARKAR[1], L. SÁNCHEZ RODRÍGUEZ[1], D. DAS[1], A. CISSE[4], Y. E. LIMA CARMONA[2], J. L. CONTRERAS-VIDAL[3];
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Abstract: EEG-based Brain-Computer Interface (BCI) systems face challenges in signal quality — susceptibility to artifacts and low signal-to-noise ratio. These limitations become pronounced when decoding motor imagery (MI), where motion artifacts can easily obscure the neural signatures. Also, most MI-based decoding studies are framed as binary classification tasks, failing to capture complex neural dynamics. For robotic-assisted gait control in particular, walk/rest classification alone cannot capture gait-phase-specific neural dynamics (Roeder et al., 2024). Hence, we propose a modular 2-block BCI architecture — a real-time denoising feature-extraction block paired with a 4-state gait decoder — validated through closed-loop deployment on a lower-limb exoskeleton.The feature-extraction block accepts EEG preprocessed via H∞ (Kilicarslan et al., 2016) and bandpass filtering. Artifact suppression via nASR (Sarkar & Contreras-Vidal, 2026) is followed by multi-domain spatial-spectral-temporal feature extraction using ROI-based spatial filtering and adaptive RDWT filtering (Sarkar et al., 2026) into δ/θ, α, and β sub-bands.The decoder block processes band-specific parallel branches, each comprising a novel Polynomial Time-Varying Layer (PolyTVL) — which extends linear time-invariant state-space models with dual learnable polynomial transforms and a time-varying state transition matrix — followed by average pooling and an LSTM sequence summarizer. Stacked LSTM outputs are decoded into four gait states: Stand, Initiate, Execute, and Terminate.An ablation study confirmed PolyTVL+LSTM (v01) as the best generalizing decoder (open-loop sessions: validation MCC: 0.435, train-validation gap: 0.187), with consistent feature discriminability across ROIs and sub-bands (Kruskal-Wallis, $p < 0.05$). Closed-loop deployment achieved 55.3% REX-assisted and 52.7% volitional gait-initiation success rates, validating the real-world feasibility of deployable lower-limb BCI control.



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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

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Topic: F.05. Brain-Machine Interface

Support: NSRF Thailand via the Research and Innovation Acceleration Agency for Competitiveness and Area Development (RCAD) (Program Management Unit for Frontier Brainpower and Future Industries) [grant number B13F690044])

Title: Motor Execution Priming Enhances Frontocentral Sensorimotor Rhythm Modulation During Motor Imagery Using a Low-Cost EEG-Based Brain-Computer Interface

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Abstract: Motor imagery (MI)-based brain-computer interfaces (BCIs) decode movement intentions through modulation of sensorimotor rhythms. However, reliable MI decoding remains challenging due to substantial inter-individual variability in MI ability and the limited sensorimotor coverage of portable EEG systems. Consumer-grade devices such as the Emotiv EPOC X do not include electrodes over canonical motor cortex locations (C3/C4), potentially reducing sensitivity to MI-related neural activity. We hypothesized that motor execution (ME) performed prior to MI would prime motor representations, enhance sensorimotor rhythm modulation, and facilitate subsequent MI-related cortical engagement. Nine healthy adults (5 females, 4 males; 23-32 years) completed an ME-primed MI protocol involving left- and right-hand motor execution followed by motor imagery. EEG signals were recorded using the Emotiv EPOC X headset. Alpha-band (8-13 Hz) event-related desynchronization (ERD) and hemispheric lateralization were evaluated at FC5 and FC6 and compared with a preliminary MI-only dataset. ME priming increased alpha-band ERD magnitude across frontocentral electrodes during both left- and right-hand imagery. During left-hand MI, ERD increased at FC5 (−17.62% vs. −14.25%) and FC6 (−21.68% vs. −15.34%). During right-hand MI, ERD increased at FC5 (−16.91% vs. −11.33%) and FC6 (−17.00% vs. −3.84%). In addition, hemispheric asymmetry was reduced following ME priming, with lateralization indices shifting toward zero during left-hand (−0.09 vs. 0.29) and right-hand imagery (0.01 vs. 0.17). This pattern suggests more balanced bilateral recruitment of frontocentral motor-planning networks following motor execution training. These findings indicate that motor execution priming enhances MI-related

cortical engagement and alters hemispheric recruitment patterns during motor imagery. The results further suggest that ME-assisted training may partially mitigate the impact of limited sensorimotor coverage in portable EEG systems and improve the robustness of low-cost MI-based BCIs.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

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Program #/Poster #: PSTR063.12/DD30

Topic: F.05. Brain-Machine Interface

Support: NSF NCS
NIH NINDS
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Simons Foundation

Title: Altering the Relative Timing of Inter-Areal Interactions using a Brain-Computer Interface

Authors: *N. LARRY[1], S. SNYDER[2], E. GOKCEN[1], A. P. BATISTA[2], S. M. CHASE[1], B. M. YU[1], M. A. SMITH[1];
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Abstract: To support our ability to perceive, think, and act, multiple brain regions cooperate and interact. Extensive research has focused on the computations that happen within each brain region. While we know much about the anatomical connections between areas, we know relatively little about the mechanisms that allow inter-areal interactions to be adjusted to the changing requirements of behavior and cognition. One key feature of these interactions is their directionality and temporal latency. While biophysical constraints on the latency between connected brain areas are on the order of several milliseconds, the effective latency for the appearance of task-relevant information can be much longer. This suggests that the latency between brain regions reflects network-level processing rather than simple conduction delays. It is currently unknown whether these latencies are fixed network properties or can be adapted to better support the requirements of a given task. One major challenge in answering this question is designing experiments that can causally manipulate these latencies.
Here, we use a brain-computer interface (BCI) approach to challenge a monkey to produce different latencies in the interactions between two cortical regions. BCI is well known for its application in motor prosthetics. However, it can also serve as a powerful tool for basic science by providing subjects with moment-to-moment feedback of their neural activity. To test the flexibility of interaction latencies, we focused on two highly interconnected cortical regions, the dorsal pre-motor cortex (PMd) and primary motor cortex (M1). We designed a dual-area BCI

task that provided a monkey with visual feedback about the activity of neural populations in these regions. To move a cursor towards a target, the monkey had to coordinate activity across the two populations so that the resulting cursor-control signals emerged with task-specified latencies. We observed that the monkey was able to modulate the latencies of interaction according to task demands. This demonstrates that the brain can flexibly orchestrate across-area interaction timing. Flexible interactions across areas may be a critical mechanism for context-dependent behavior and learning that builds on well-studied within-area mechanisms.

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Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.13/EE1

Topic: F.05. Brain-Machine Interface

Support: JST PRESTO Grant Number JPMJPR23I1 Japan

Title: EEG aperiodic activity is associated with intracortical facilitation in the human motor cortex

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Abstract: Scale-free 1/f-like activity is a prominent feature of neural electroencephalographic (EEG) signals and has been proposed to reflect excitatory-inhibitory circuit state. However, direct physiological evidence for this interpretation in the human motor cortex remains limited. Here we combined real-time electroencephalographic neurofeedback with transcranial magnetic stimulation to test whether motor cortical states characterized by distinct aperiodic exponents are associated with corresponding differences in intracortical physiology. Participants were guided to self-modulate sensorimotor activity toward relatively flatter or steeper aperiodic states while transcranial magnetic stimulation (TMS) was delivered contingent on the ongoing EEG activity. Offline analyses confirmed reliable separation of the aperiodic exponent between states (paired *t*-test, $p < 0.001$, $d = -3.9$), whereas alpha-band activity did not differ (paired *t*-test, $p < 0.748$, $d = 0.06$), suggesting that the manipulation primarily targeted the aperiodic exponent rather than alpha-band oscillatory activity. Critically, intracortical facilitation (ICF) was selectively reduced during steeper aperiodic states (rmANOVA with post hoc *t*-test, $p < 0.037$, $d = 0.27$), indicating that aperiodic state differences were accompanied by changes in excitatory intracortical circuit function. These findings provide physiological evidence that the EEG aperiodic exponent tracks excitatory intracortical circuit function in the human motor cortex, independent of conventional alpha-band activity.

Disclosures: S. Mutsuda: None. **S. Iwama:** None. **J. Ushiba:** None.

Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant P41 EB018783
UK Research and Innovation (UKRI) Turing AI Fellowship 2021-2025 funded by the EPSRC under Grant number EP/V025724/1

Title: From Decoding to Negotiation - Natural Heksor/Synthetic Heksor Co-Adaptation During Three-Dimensional Motor-Imagery BCI Learning: Methods Development

Authors: D. COYLE[1], *N. DU BOIS[2], T. M. VAUGHAN[3], J. R. WOLPAW[4];
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Abstract: Brain-computer interfaces (BCIs) are often seen as neural activity decoders. Recent theory suggests BCIs instead create synthetic heksors: adaptive systems comprising CNS activity and machine learning. If BCIs are to be as reliable as muscles, they must negotiate effectively with the pre-existing natural heksors with which they share neurons & synapses (For review: doi.org/10.1088/1741-2552/addd47). To achieve this, we are developing a framework to study natural/synthetic heksor negotiation during 3D upper-limb motor imagery BCI learning (see: doi.org/10.48550/arXiv.2605.29677).

Healthy people perform actual hand movements and motor imagery BCI control, toward common 3D reaching targets while high-density EEG, EMG, and motion capture are recorded. Training occurs in immersive VR with an embodied virtual hand. Movement execution and motor imagery BCI-control trials alternate around identical targets. Movement trials give EEG, EMG, and kinematic representations of natural heksor activity. BCI trials require control of the virtual hand with EEG-derived activity. Rather than treating movement and imagery as independent controllers, AI decoders learn movement-derived, imagery-derived, and shared latent representations. Sequential training, in which movement representations are acquired before BCI training, is compared with parallel training, in which movement and BCI-control trials alternate. Initial results support protocol feasibility.

Negotiation will be manipulated through progressive assistance, from 100%-assisted trajectory replay to self-generated BCI control (0% assistance). Intermediate levels create shared-control in which natural and synthetic heksors jointly determine behavior. We hypothesize that actual movement and motor imagery are complementary expressions of a natural heksor. We expect that: (1) shared movement-imagery representations will be a better substrate for synthetic heksor

development than motor imagery alone; (2) parallel movement-BCI learning will promote better negotiation than sequential learning; and (3) gradual reduction of assistance will create a more stable negotiated equilibrium than abrupt transition to full BCI control. Negotiation is quantified using decoder stability, learning rate, embodiment, sensorimotor coupling, variability, transfer, and retention. This framework shifts BCI research from maximizing decoding accuracy toward understanding how adaptive artificial systems integrate with neural control architectures. It has translational relevance for neurorehabilitation that combines attempted movement, motor imagery, and exoskeleton-assisted feedback.

Disclosures: D. Coyle: Other; University of Bath. **N. du Bois:** None. **T.M. Vaughan:** None. **J.R. Wolpaw:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.15/EE3

Topic: F.05. Brain-Machine Interface

Support: National Science and Technology Innovation 2030 Major Program grant 2022ZD0210300

Title: Neuronal encoding changes during long-term Brain-Machine Interface operant conditioning task

Authors: *T. MA[1,2,3], C. WANG[1,3], C. REN[1,3], Z. ZHAO[1,2,3];
[1]Inst. of Neuroscience,Chinese Acad. of Sci., Shanghai, China; [2]Univ. of Chinese Acad. of Sci., Beijing, China; [3]Ctr. for Excellence in Brain Sci. and Intelligence Technology, Chinese Acad. of Sci., Shanghai, China

Abstract: How neural circuits support motor brain-machine interface (BMI) learning remains debated: do animals primarily rely on global recruitment of broad neural populations or on local refinement of task-relevant neurons? Here, we used an auditory motor BMI paradigm in adult male C57 mice to examine long-term changes in primary motor cortex (M1), secondary motor cortex (M2), and dorsolateral striatum (DLS) during BMI task learning. Four mice were reported, trained for 11-15 days, and chronically recorded with ultra-flexible electrodes. Animals controlled auditory frequency by modulating the firing-rate difference between two M1 neuron groups, with feedback mapped to seven discrete tones spanning 5-19 kHz. Across training, performance improved from 40% correct in early sessions to 90% in late sessions, while the median time to success decreased from 12 s to 4 s. We recorded 264 units in M2, 327 units in M1, and 225 units in DLS (0.64 units/channel on average), and matched 164 same units across learning stages.
To quantify auditory responsiveness, we fit a Poisson generalized linear model (GLM) and compared observed model R^2 values with shuffle distributions generated by randomizing spike

counts. Neurons were classified as auditory responsive or nonresponsive, and responsive neurons were further categorized as monotonically increasing, monotonically decreasing, peak, or unclassified. Classification was based on Friedman tests, Spearman rank correlations, quadratic fits, and permutation testing. Auditory-tuned neurons were present in 35%, 29%, and 28% of units in M2, DLS, and M1, respectively, during early learning; these proportions increased to 48%, 30%, and 46% in mid learning, then decreased to 15%, 19%, and 24% in late learning. In parallel, selectivity index increased across training, indicating more selective frequency coding. Longitudinal analysis of matched units showed that task-related firing emerged primarily during early and late trial epochs in late learning, with ~30% of neurons exhibiting significant stage-dependent modulation during early trial periods.
These findings suggest that motor BMI learning initially engages broad exploratory population activity, followed by a refinement toward more selective and efficient coding, with direct neurons becoming increasingly task-locked during skilled performance.

Disclosures: T. ma: None. **C. Wang:** None. **C. Ren:** None. **Z. Zhao:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.16/EE4

Topic: F.05. Brain-Machine Interface

Support: 2022ZD0210300

Title: Investigating the Co-Adaptation Mechanisms for Motor Brain-Computer Interfaces

Authors: *G. CHEN[1], Z. ZHAO[2];
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Abstract: Background: Conventional closed-loop brain-computer interfaces (BCIs) rely heavily on naturally mapping innate motor cortical tuning. However, constrained by biological representations, pure natural mapping restricts the control of high-dimensional, non-natural devices. Neural co-adaptation serves not merely as a passive stabilization mechanism, but as a core pathway to bypass these constraints. We investigated motor cortical dynamic compensation under specific decoder perturbations and explored "targeted induction" by repurposing perturbed units to command non-natural control dimensions.
Methods: Using flexible electrodes in a macaque monkey, we recorded single-unit activity from the primary motor cortex (M1). We implemented a Velocity Kalman Filter (VKF) to decode real-time kinematics during a continuous motor task. Upon achieving stable baseline performance, we introduced a "Unit Drop" perturbation, eliminating the decoder weights for 10% of recorded units, to disrupt the natural mapping equilibrium and track the ensuing population dynamics.

Results: Exponential models indicated that post-perturbation, neural decoding performance recovered within ~30 blocks, defined by the signal-to-noise ratio (SNR) stabilizing above 85% of baseline. Structured subpopulation dynamics drove this recovery. "Bone-anchor" units sustained stable low-dimensional manifolds; units with robust initial task tuning (modulation depth [MD], R^2) and superior functional weight (Potent Ratio, Top-3 Loading) demonstrated highly stable preferred directions (PD) (all $p < 0.001$). Units possessing initially strong tuning exhibited profound plasticity (absolute changes in MD and R^2 correlated positively, $p < 10^{-7}$). Through functional reconfiguration, the repurposed units rapidly acquired stable closed-loop control over an entirely independent task dimension (cursor diameter scaling) within 15 blocks, surpassing a rigorous >95% task success rate criterion. Ongoing work evaluates simultaneous 2D kinematic and 1D scale control.
Conclusion: The motor cortex dynamically compensates for decoder perturbations via structured subpopulation adjustments, utilizing immense plasticity to establish novel control dimensions. Actively repurposing neural resources via targeted induction enables neural populations to transcend innate physical limits, offering direct neurophysiological evidence to guide the development of next-generation, high-degree-of-freedom BCIs.

Disclosures: G. Chen: None. **Z. Zhao:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.17/EE5

Topic: F.05. Brain-Machine Interface

Title: One platform, many applications: a modality-agnostic architecture unifying EEG, ECG, and EMG across neuroscience, rehabilitation, and BCI

Authors: *A. ASOPA[1], S. BHATTACHARJEE[2];
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Abstract: Biosignal acquisition has long forced researchers and developers to trade fidelity against accessibility and flexibility. Research-grade hardware exceeds $30,000, is typically single-modality, and fixes channel count and placement; low-cost consumer devices sacrifice signal fidelity; and commercial applications often demand different hardware for each use case. At Anthriq we attempted to create one architecture that delivers research-grade EEG, ECG, and EMG at any scale and form factor, even under these constraints.The system uses a three-tier design—electrode-level conditioning, regional digitization, and central coordination—enabling simultaneous EEG, ECG, and EMG recording with programmable gain spanning microvolts to millivolts and scalable channel counts from 4 to 128. Signal fidelity was benchmarked against published low-cost and research-grade EEG datasets across noise floor, alpha SNR, SSVEP SNR, and the aperiodic (1/f) exponent, with performance matching research-grade systems across all metrics. Alpha modulation and SSVEP paradigms produced clean spectral peaks well

above baseline.An ongoing multimodal study examines the effects of short diurnal sleep on performance in cognitively demanding tasks, using 13-channel EEG to capture spectral dynamics across sleep and post-sleep cognitive load conditions. Pilot data demonstrate the platform's capacity to resolve task-relevant spatiotemporal features in within-subject comparisons, with full data collection underway.We further validated practical utility through Project Kinesis, recording 13-channel forearm sEMG from 50 participants across an expanded set of hand gestures spanning basic, communicative, directive, and device-interactive movements. Correlation structure tracked shared and antagonistic muscle recruitment, and classification reached 85-95% within-participant and 60-70% across participants.Synchronized tri-modal recording across EEG, ECG, and EMG confirms time-aligned multimodal capture within a single acquisition session. The architecture is currently being applied to closed-loop motor rehabilitation, autonomic and sleep monitoring, and embodied-cognition paradigms requiring simultaneous brain and body recording. By consolidating research-grade multimodal acquisition into one configurable platform, the system lowers the barrier to complex biosignal research and extends naturally to a broad range of neuroscience, clinical, and BCI applications.

Disclosures: A. Asopa: A. Employment/Salary (full or part-time):; Researcher at Anthriq India.
S. Bhattacharjee: A. Employment/Salary (full or part-time):; Anthriq India.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.18/EE6

Topic: F.05. Brain-Machine Interface

Title: Decoding mechanisms of micturition in the human brain during bladder filling and emptying using functional ultrasound imaging

Authors: *K. A. AGYEMAN[1], D. J. LEE[2], H. ZAREIAN[3], E. KREYDIN[1], C. LIU[4], V. N. CHRISTOPOULOS[3];
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Abstract: Lower urinary tract dysfunction remains inadequately treated yet affects over 30 million adults in the United States. Current care mostly focuses on symptom management rather than restoration of normal bladder sensation and function. In part, because most of the mechanistic understanding of micturition is derived from animal studies with minimal validation from humans, due to constraints inherent to conventional functional neuroimaging. Consequently, while the pontine micturition center (PMC) and periaqueductal gray (PAG) serve as critical relay and integration hubs for coordinating micturition, their functional mechanisms and dynamics remain poorly defined in humans. Here, we utilize functional ultrasound imaging (fUSI) to characterize dynamics of the human brainstem underlying micturition and to decode bladder pressure (BP) from brain activity. To this end, we acquired fUSI recordings through a cranial window, simultaneously with BP signals during controlled bladder filling and emptying -

intraoperatively from three patients undergoing standard-of-care Chiari decompression surgery under general anesthesia (Fig. 1ABCD). A linear support vector machine regression model trained on fUSI power Doppler and BP signals accurately reconstructed bladder pressure changes and revealed cerebellar and midbrain (PMC, PAG) regions where the hemodynamic signal strongly correlates with bladder pressure (Fig. 1 EFG). Interestingly, in assessing the temporal effects of micturition on local neural connectivity and energy dynamics, we found strong generalized regional decrease in local connectivity during bladder filling and emptying, but distinct dynamic local network-level alterations in autocorrelation function and pD residuals signal energy in cerebellar, PMC and PAG regions (Fig. 1H). Together, our study provides a first inhuman application of fUSI for deciphering neural mechanisms of the brain during micturition - providing proof-of-concept for ultrasound-based brain machine interfaces aimed at restoring bladder function in neurogenic bladder disorders.

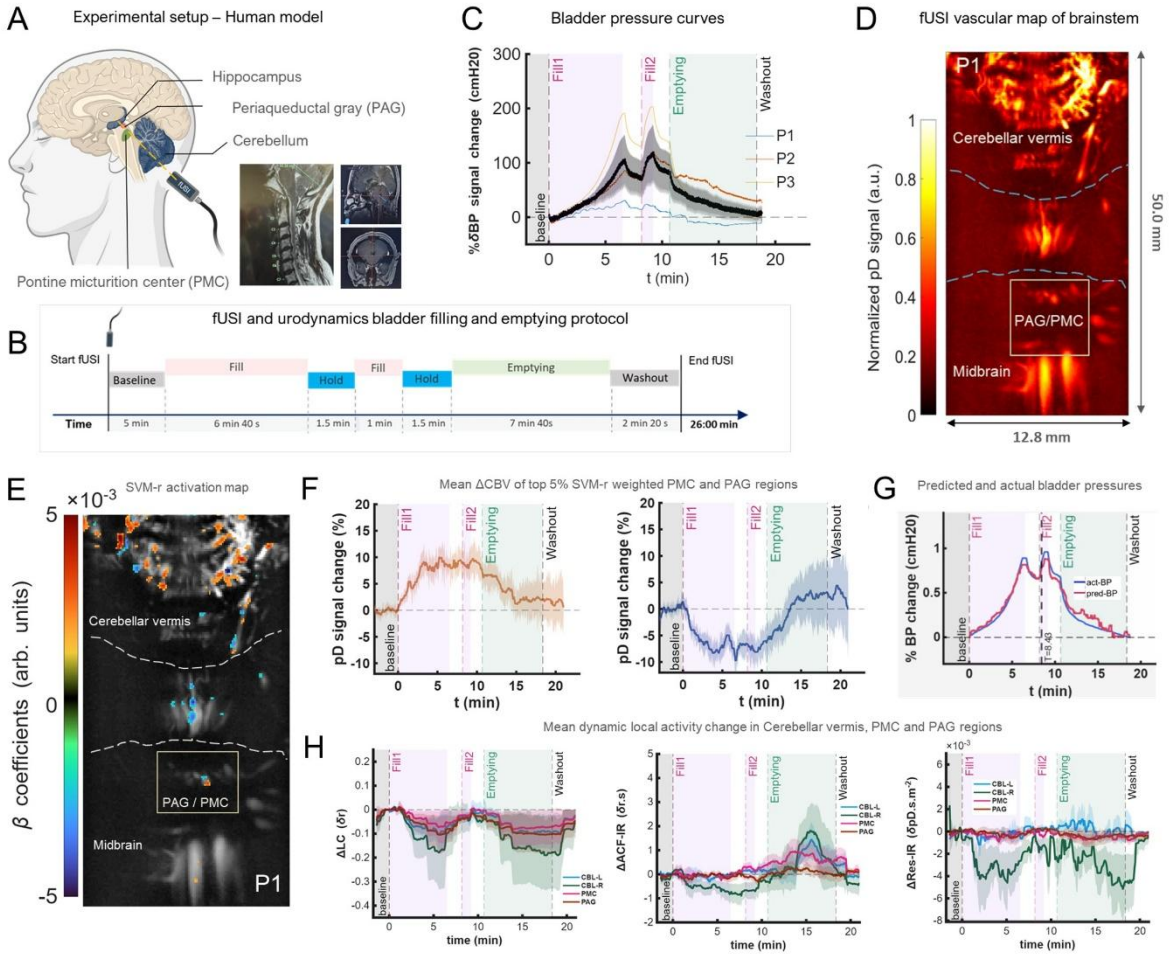


Figure 1: A) Model for studying micturition evoked effects in the human brain. **B)** Experimental protocol for simultaneous fUSI of the brainstem and bladder filling and emptying. **C)** Percentage change of bladder pressure signals over time for three patients. **D)** fUSI power Doppler 2D vascular map of the brain (representative patient). **E)** SVM-r weighted map of micturition related brain regions (patient P1) overlayed on fUSI pD greyscale background image. **F)** Average change in cerebral blood volume (ΔCBV) of PMC and PAG midbrain regions identified by SVM-r that are positively (orange curve) and negatively (blue curve) correlated with BP from panel E. **G)** Actual (blue curve) and SVM-r reconstructed (red curve) bladder pressures. **H)** Curves of the dynamic local connectivity (LC), autocorrelation function impulse response (ACF-IR) and pD residuals impulse response (Res-IR) measures of local neural activity and signal energy changes relative to baseline activity using 3-min data frames at 10 s sliding window steps, for cerebellar (green and blue curves, left and right sides respectively), PMC (light red curves) and PAG (brown curves) regions, across all patients.

Disclosures: K.A. Agyeman: None. **D.J. Lee:** None. **H. Zareian:** None. **E. Kreydin:** None. **C. Liu:** None. **V.N. Christopoulos:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.19/EE7

Topic: F.05. Brain-Machine Interface

Support: NIH Grant R01-DC019498

Title: Shared latent representations of speech production for cross-patient speech decoding

Authors: *Z. SPALDING[1], S. DURAIVEL[1], S. RAHIMPOUR[3], C. WANG[1], K. BARTH[1], C. SCHMITZ[1], S. LAD[2], D. G. SOUTHWELL[2], J. VIVENTI[1], G. B. COGAN[2];
[1]Biomed. Engin., [2]Neurosurg., Duke Univ., Durham, NC; [3]Neurosurg., Univ. of Utah, Salt Lake City, UT

Abstract: Speech brain-computer interfaces (BCIs) offer a critical pathway to restoring communication for individuals unable to speak due to neuromotor disorders such as amyotrophic lateral sclerosis (ALS) and brainstem stroke. However, current speech BCIs face significant barriers to widespread clinical adoption, most notably their dependence on large volumes of patient-specific training data that must be collected over extended periods of time. A promising solution to facilitate usability and accelerate their successful deployment is to combine data from multiple patients. This has proven difficult, however, due to differences in user neuroanatomy, varied placement of electrode arrays, and sparse sampling of targeted anatomy. To address these obstacles, we aligned patient-specific neural recordings to a shared latent space, enabling speech BCIs to be trained on data combined across patients. Patient-specific neural signals were collected intraoperatively with high-density micro-electrocorticography (μECoG) arrays from eight patients performing a speech repetition task. Leveraging canonical correlation analysis (CCA) to perform alignment to a shared space, we identified shared neural latent dynamics that preserved fine-grained, micro-scale speech information across all eight patients. Crucially, this approach enabled cross-patient decoding models to achieve improved phoneme decoding accuracy relative to patient-specific models ($p = 0.01$, two-sided paired t-test, patient-specific mean: 24%, cross-patient mean: 31%, chance 11%). We found the cross-patient improvements were facilitated by the high resolution and broad coverage of μECoG. Further, we validated the translational feasibility of cross-patient speech decoding using simulated real-time neural recordings and a streaming recurrent neural network (RNN) to decode phoneme identity. Models trained on cross-patient data achieved lower phoneme error rate (PER) than patient-specific models ($p = 0.02$, two-sided Wilcoxon signed-rank test, patient-specific: 87.1%, cross-patient: 79.4%, chance: 88.4%). These results demonstrate that neural representations of speech, while

individually variable at the surface level, contain a shared structure that can be harnessed across patients. Our findings support future speech BCIs that are more accurate and rapidly deployable, ultimately improving the quality of life for people with impaired communication from neuromotor disorders.

Disclosures: Z. Spalding: None. **S. Duraivel:** None. **S. Rahimpour:** None. **C. Wang:** None. **K. Barth:** None. **C. Schmitz:** None. **S. Lad:** None. **D.G. Southwell:** None. **J. Viventi:** None. **G.B. Cogan:** None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.20/EE8

Topic: F.05. Brain-Machine Interface

Title: A Signal Processing method based on Striatal Beat Frequency banking and correlation coefficients as an aid to improve classification methods for Brain-Computer Interfaces in the context of BCI Competition EEG datasets specific to responses to intensifications of alpha-numeric characters in a matrix

Authors: *J. LARUE;
James LaRue dba Jadco Signals, Hanahan, SC

Abstract: This paper demonstrates a method for time-domain analysis of an electroencephalogram (EEG) using the theory of interval timing and Striatal Beat Frequency (SBF). We form a bank of single-period single-frequency (SPSF) sinusoids where the number of points making up each SPSF sinusoid is commensurate with the EEG device sampling rate. We previously demonstrated our method at Society for Neuroscience 2023 in the context of detecting epileptic seizures, and possibly more importantly, the precise detection of the aura via a moving 2 Hz SPSF that preceded the actual seizure. In this paper we apply the same SPSF approach in the context of Brain-Machine Interfacing by utilizing BCI Competition datasets focused on recorded electro-encephalogram (EEG) responses to intensifications of 36 alpha-numeric characters arranged in a 6x6 matrix. While the paper contrasted SPSF to two other popular methods, specifically Morley Wavelets and Sliding-window FFTs, we will instead focus on how we first imposed strict segmentation rules involving the EEG data recorded from the nodes and separate tests, the determination of reliable start-stop time intervals of character row/column intensifications, and limitations imposed on the SPSF algorithm due to sampling rate and band-pass filtering.

Disclosures: J. LaRue: None.

Poster

PSTR063: BMI Neurophysiology: Decoding, Neurophysiology, and Processing I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR063.21/EE9

Topic: F.05. Brain-Machine Interface

Title: Cross-Dataset Generalization of a Motor Imagery Index for BCI Literacy Prediction

Authors: A. AHARONYAN[1], M. PUTZOLU[2], E. PELOSIN[2], S. ANWAR[3], *A. VATO[1]; [1]The Catholic Univ. of America, Washington, DC; [2]Dept. of Neuroscience, Rehabilitation, Ophthalmology, Genet. and Maternal and Child Sci., Univ. of Genoa, Genoa, Italy; [3]Div. of AI Res., Children's Natl., Washington, DC

Abstract: Background: Motor Imagery-based brain-computer interfaces (MI-BCIs) hold great potential as a tool for functional rehabilitation across different neurological disorders. The effective utilization of BCIs critically depends on individual differences, which are reflected in variability in BCI literacy. It is usually assessed indirectly through task performance or extensive system calibration, and there currently exists no objective neurophysiological marker for screening. To address this limitation, this study investigates whether a deep learning (DL) model trained on electroencephalographic (EEG) data collected in a Parkinson's disease (PD) motor imagery study can serve as a generalizable marker of BCI literacy. Methods: A DL model was trained using 128-channel EEG recordings collected during MI tasks from healthy and PD individuals. Model outputs were transformed into a continuous subject-specific Motor Imagery Index (MII) to quantify the strength and quality of motor imagery-related neural activity. The original recordings were then reduced to a standard 62-channel montage, and a smaller model was trained. This model was applied to the OpenBMI dataset (doi:10.5524/10054), which extracts BCI literary scores by testing three major BCI paradigms with 54 healthy participants. Results: The MII showed a significant positive association with independently measured BCI literacy scores ($r = 0.48$, $p < 0.001$) and accounted for 23% of the variance in BCI literacy ($R^2 = 0.23$). It significantly differentiates high- and low-literacy groups (Cohen's $d = 0.72$, $p < 0.01$), suggesting potential utility for coarse-grained screening of MI proficiency. Performance remained stable when reducing the number of channels from 128 to 62, while classification accuracy decreased from 0.82 to 0.79. Spatial analysis indicated that the most informative contributions were concentrated over sensorimotor regions (notably C3, Cz, and C4 neighborhoods). Conclusions: Our motor imagery index provides a generalizable EEG-based marker and serves as a simple screening tool for BCI literacy. Its robustness to electrode reduction suggests it can be obtained with low-density, affordable EEG systems, enabling rapid, accessible screening and reducing the need for extensive calibration. Such lightweight assessment protocols have the potential to significantly lower barriers to adoption of BCI-based neurorehabilitation in both clinical settings and underserved populations. Furthermore, reliable screenings for BCI literacy may encourage patients to pursue treatment, addressing confidence loss, one of the largest barriers to effective rehabilitation.

Disclosures: A. Aharonyan: None. **M. Putzolu:** None. **E. Pelosin:** None. **S. Anwar:** None. **A. Vato:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

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Program #/Poster #: PSTR064.01/EE10

Topic: G.03. Stress and the Brain

Support: NSF Grant IOS-2445004
NSF Grant IOS-1845020

Title: Expression of the tardigrade protein Dsup in C. elegans neurons protects from UV-induced DNA damage and alters sleep

Authors: *G. GAZZARA[1], M. NELSON[2];
[1]St. Josephs Univ., Philadelphia, PA; [2]Biol., St. Joseph's Univ., Philadelphia, PA

Abstract: Sleep is essential and the mechanisms controlling it are conserved. Numerous functions for sleep have evolved which include energy conservation, metabolic compartmentalization, memory consolidation, and recovery from illness. Sleep also supports repair in response to DNA damage, a homeostatic driver of sleep, and may represent one of sleep's basal functions (Zada et al. 2022. Mol Cell). The nematode C. elegans displays prominent sleep in response to ultraviolet (UV) irradiation (i.e., UV-sleep), which requires components of DNA damage response pathways (DeBardeleben et al. 2017. Genetics). This UV-sleep provides a powerful model for mechanistic sleep studies at the circuit and single cell level, considering it is largely controlled by two neuropeptidergic interneurons called ALA and RIS (Hill et al. 2014; Konietzka et al. 2020. *Current Biology*), within a compact 302-celled nervous system. In this simple cellular framework however, a complex array of signaling molecules exist, and many mechanistic questions remain unanswered.
Many organisms have evolved protective mechanisms against UV irradiation and DNA damage, with Tardigrades (i.e., water bears) representing an extreme example. These hardy microscopic animals are famous for their ability to resist noxious conditions, such as high heat and intense UV light. Tardigrades express a unique protein called damage suppressor (Dsup), which binds DNA (Hashimoto et al. 2016. Nat Comm), absorbs UV light, and mitigates damage (Chavez et al. 2019. eLife). We sought to use Dsup to further characterize these protective effects in vivo, and to determine where DNA damage is being sensed in C. elegans during UV-sleep. To do this we expressed a C. elegans codon-adapted Dsup, which was fused with gfp, in C. elegans. It was expressed in all cells, and then in subsets of tissues: nervous system, skin, body-wall muscle, pharyngeal muscle, and intestine, and then we measured UV-sleep, as well as the worm's response to noxious heat. We found that Dsup localizes to the nucleus in C. elegans, and has unique effects in different tissues. When Dsup was expressed in all cells, UV-sleep was surprisingly enhanced, indicating that susceptibility to damage was increased, and their behavioral response to high heat was exacerbated. However, when Dsup was selectively expressed in body-wall muscle or the nervous system, UV-sleep was reduced, supporting a protective function for Dsup in excitable cells. Expression in the skin protected the animals from noxious heat. These experiments suggest that Dsup may function differently depending on the

cellular context, and that C. elegans is particularly sensitive to UV damage in muscle and neurons.

Disclosures: G. Gazzara: None. **M. Nelson:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.02/EE11

Topic: G.03. Stress and the Brain

Title: The Role of TMEM132Bb Interaction with GABAA Receptors in Activation by GABA, Propofol, and Diazepam

Authors: *Z. ZHANG;
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Abstract: The ascending reticular activating system in the brain stem has been recognized as a primary network essential for the re-emergence of consciousness from anesthesia. Among the nuclei in the brain stem, the parabrachial nucleus is a pivotal component that controls behavioral wakefulness and electroencephalographic arousal. However, the upstream nuclei that innervated the pararbrachial nucleus and their roles in anesthesia remains unknown. This study found an upstream nucleus of the medial parabrachial nucleus (MPB) and its role under sevoflurane anesthesia. Method In this study, C-fos staining and electrophysiological recordings from brain sections were used to assess neural activity in the dorsal mesencephalic nucleus (dDpMe) following sevoflurane exposure. Chemogenetic and optogenetic manipulations were performed via AAV injections in Vgat-Cre mice to regulate the activity of dDpMe GABAergic neurons. Additionally, the loss of righting reflex (LORR) and EEG monitoring were employed to evaluate anesthetic states, while fluorescent tracing was used to map neural projections. Results We show that GABAergic neurons in the dorsal mesencephalic nucleus (dDpMe) exhibit enhanced activation during sevoflurane exposure. We further demonstrate that chemogenetic or optogenetic activation of dDpMe GABAergic neurons enhances the anesthetic effects of sevoflurane, whereas inhibition of these neurons attenuates the anesthetic effect. Moreover, we traced the major projection from dDpMe GABAergic neurons to contralateral glutamatergic neurons in the medial parabrachial nucleus (MPB) rather than to the lateral hypothalamus (LH). **Discussion** We identified the dDpMe as a critical inhibitory target of PBN glutamatergic neurons, bridging the gap between upstream circuits and established arousal pathways. Furthermore, we discussed the distinct functions of the dorsal and ventral mesencephalic nuclei, as well as the synaptic connectivity of dDpMe GABAergic neurons.

Disclosures: Z. Zhang: None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.03/EE12

Topic: G.03. Stress and the Brain

Support: NIH Grant R01ES035851
NIH Grant P20GM139753

Title: Subtoxic Methylmercury Preferentially Inhibits Thioredoxin Reductase

Authors: *C. MA[1], M. WATANABE[3], K. WURLITZER[3], M. W. PITTS[2];
[2]Dept. of Cell and Mol. Biol., [1]Univ. of Hawaii, Honolulu, HI; [3]Cell and Mol. Biology, John A. Burns Sch. of Med., Univ. of Hawai'i at Manoa, Honolulu, HI

Abstract: Environmental exposure to methylmercury (MeHg) is a global health concern due to its potent neurotoxicity. Consumption of aquatic products is the primary route of human exposure. MeHg has a long biological half-life and low clearance rate, allowing it to accumulate in the body over time. Although MeHg-induced neurotoxicity has been widely reported, the underlying molecular mechanisms remain incompletely understood. Thioredoxin reductase (TXNRD) and glutathione peroxidase (GPX) are two major selenoenzymes that play essential roles in antioxidant defense and redox regulation. Previous studies have shown that MeHg inhibits both TXNRD and GPX at high concentrations (>1000nM). In this study, we examined the effects of MeHg at subtoxic concentrations (200-1000 nM) upon selenoenzyme activity and redox homeostasis in three neuronal cell lines (mHypoE-44, HT-22, and SH-SY5Y). Cells were challenged with MeHg or selenium deficiency for 18 hours, followed by assessment of TXNRD and GPX activities. We also employed Fast-TRFS, a fluorogenic probe of TXNRD, to evaluate the immediate effect of MeHg exposure on TXNRD activity in live cells. In parallel, we performed *in vivo* studies where mice were fed MeHg-containing chow from 3 to 8 weeks of age, followed by measurement of TXNRD activity, GPX activity, and concentrations of selenium and mercury in whole brain tissue. Our results showed that subtoxic doses of MeHg selectively inhibit TXNRD activity in three neuronal cell lines and mouse brain tissue. In contrast, GPX activity was more closely associated with the level of selenium supplementation rather than amount of MeHg exposure. Fast-TRFS assay revealed that the inhibitory effect of MeHg on TXNRD activity can be detected as early as 1 hour after exposure to subtoxic dose of MeHg. Protein expression of TXNRD1 and TXNRD2 was not altered by MeHg treatment, suggesting that the inhibition occurs at functional level rather that reduced protein synthesis. These findings indicate that MeHg preferentially inhibits thioredoxin reductase activity in both *in vitro* and *in vivo* models. Further studies will investigate the molecular signaling pathways through which disruption of the thioredoxin system by subtoxic MeHg contributes to neurotoxicity.

Disclosures: C. Ma: None. **M. Watanabe:** None. **K. Wurlitzer:** None. **M.W. Pitts:** None.

Poster

PSTR064: Stress: Cellular Actions

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.04/EE13

Topic: G.03. Stress and the Brain

Support: Fondation de France
SPARK
Inserm Transfert

Title: Glucocorticoid-Induced PAI-1 dysregulation following traumatic stress: Implications for PTSD

Authors: *S. ABDELKAOUI, M. MENNESSON, M. VALLEE, S. TRONEL, A. DESMEDT, J.-M. REVEST;
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Abstract: Post-traumatic stress disorder (PTSD) is a psychiatric disorder that may develop after exposure to traumatic events. PTSD is characterized by emotional dysregulation, maladaptive memory processing and structural brain alterations, including reduced hippocampal volume1,2. Despite extensive clinical characterization, the neurobiological mechanisms linking traumatic stress to hippocampal dysfunction remain poorly understood. This project investigates the role of Plasminogen Activator Inhibitor-1 (PAI-1), a stress-responsive inhibitor of the tissue Plasminogen Activator (tPA)/plasmin pathway, in PTSD-like memory impairment in mice. Previous preclinical findings from our laboratory showed that glucocorticoid-induced PAI-1 promotes PTSD-like memory through an impairment of the pro-BDNF/m-BDNF balance3. In addition, using a translational approach combining longitudinal cohort of human subject's observations and mechanistic cellular analyses, we recently found that circulating PAI-1 levels were increased in military personnel who developed PTSD symptoms after deployment and correlated with symptom severity4. Here, our aim is to investigate the downstream molecular and cellular targets involved in this debilitating condition. We hypothesized that excessive PAI-1 activation contributes to pro-BDNF accumulation, activation of apoptotic pathways, astrocytic dysfunction, resulting in structural brain remodeling. In adult male and female mice exposed to a validated PTSD-like memory paradigm5, histological analyses revealed reduced GFAP-positive astrocytic area in the dorsal hippocampus and amygdala of PTSD-like mice. Ex vivo primary hippocampal cultures identified astrocytes as a direct target of PAI-1 signaling since recombinant PAI-1 was able to increase the pro-BDNF/m-BDNF ratio, to reduce astrocytic viability, and to promote apoptosis, whereas neurons were largely unaffected. Consistently, corticosterone exposure increased PAI-1 expression, pro-BDNF accumulation, and activation of stress-related apoptotic pathways. Conversely, full genetic deletion or pharmacological inhibition of PAI-1 prevented PTSD-like memory formation. Together these findings suggest astrocytes as a potential key cellular substrate of PAI-1 action and support a mechanism whereby stress-induced PAI-1 dysregulation promotes glial alterations to increase PTSD-like memory further explaining brain alteration. These results suggest that PAI-1 could be a therapeutic target for trauma-related

disorders. References: 1.Gilbertson et al 2002, 2.Bremner et al 2001, 3.Bouarab et al 2021, 4.Mennesson et al 2026, 5.Kaouane et al 2012

Disclosures: S. Abdelkaoui: None. **M. Mennesson:** None. **M. Vallee:** None. **S. Tronel:** None. **A. Desmedt:** None. **J. Revest:** None.

Poster

PSTR064: Stress: Cellular Actions

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Topic: G.03. Stress and the Brain

Support: (CDMRP) PR210574
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1R21AG091052-01A1

Title: Regulation of Anxiety-like Behavior by Angiotensinogen-Expressing Astrocytes in Brainstem

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Abstract: Background: Astrocytes are highly heterogeneous, varying in morphology, molecular identity, and function across brain regions. Understanding this diversity is essential for defining their roles in neural circuits and neuropsychiatric disorders such as anxiety. Angiotensinogen (Agt), the precursor of the renin-angiotensin system, is well known for cardiovascular functions but is also abundantly expressed in diencephalic and brainstem astrocytes, including GFAP-negative populations. Despite this distinct regional expression and its use as an astrocyte marker, its brain function remains unclear. We hypothesized that Agt^+ astrocytes form a specialized subpopulation with unique regional features that regulate anxiety-like behavior. **Methods:** Agt mRNA distribution was assessed using multiplex RNAscope™ and single-cell RNA-seq analysis of adult mouse diencephalon (Ohlig et al., 2021), visualized via UMAP with cell-type annotation using marker-based labeling (scType). Region-specific Agt deletion was achieved by injecting Cre-expressing AAV into the periventricular region of the fourth ventricle in Agt-flox mice (n = 5-6/sex). Anxiety-like behavior was measured using the elevated plus maze (EPM) at baseline and after restraint stress. **Results:** RNAscope™ revealed enriched Agt expression in peri-fourth ventricular regions, including the parabrachial nucleus, locus coeruleus, and tegmental nucleus. Single-cell analysis confirmed astrocyte-associated Agt expression across diencephalic clusters. Agt mRNA co-localized with GFAP but not NeuN, indicating astrocytic specificity in both sexes. Behaviorally, males with Agt deletion showed increased baseline anxiety (open arm time: control 146.9 ± 5.5 vs. Agt-deleted 82.8 ± 15.4; $p < 0.01$), whereas females showed no baseline

change. Following restraint stress, both sexes exhibited a trend toward increased anxiety with Agt deletion (males p = 0.08; females p = 0.09). **Conclusion:** Astrocytic Agt regulates anxiety-like behavior in a sex- and stress-dependent manner, with significant effects in males at baseline. These findings identify Agt^{+} astrocytes as a functionally distinct population and implicate astrocytic Agt in emotional regulation, potentially via astrocyte activation, neuroinflammation, or sex-dependent stress-responsive pathways. Further mechanistic studies may reveal novel therapeutic targets for anxiety disorders.

Disclosures: Z. Yu: None. **S. Martinez:** None. **A. Dunn:** None. **C. Falcone:** None. **A. Horvath:** None. **P.J. Marvar:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.06/EE15

Topic: G.03. Stress and the Brain

Support: GM152386 NIGMS IMSD T32
AA029972 NIAAA INIA Stress U01
AA010761 NIAAA ARC P50

Title: Physiological and transcriptomic adaptations in prelimbic stress-sensitive neurons following chronic stress and ethanol exposure

Authors: *G. P. SCHELDRUP, L. LEMASTER, C. COOPER, J. CROWLEY, Z. HUNTER, S. BERTO, J. A. RINKER;
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Abstract: The prelimbic medial prefrontal cortex (PL) is critical for stress regulation, and its dysfunction is implicated in alcohol use disorder (AUD). Corticotropin-releasing hormone-expressing interneurons (CRH-INs) represent a unique and understudied population of stress- and alcohol-sensitive INs in the PL. CRH-INs are highly stratified within the PL, with distinct bands of cells concentrated in layer (L) 2/3 and with a more diffuse population throughout L5/6. Preliminary data from our lab indicate that, independent of cortical layer, PL CRH-INs show an overall hyperexcitable phenotype following chronic alcohol and stress, and Crh knockdown in the PL blocks escalation of alcohol consumption. However, since INs in different layers gate distinct targets, it is critical to understand if and how CRH-INs respond differentially to alcohol and stress in L2/3 vs L5/6. We aimed to characterize alcohol- and stress-induced changes in the electrophysiological and transcriptional landscapes of PL CRH-INs across cortical layers. Adult male and female Crh-IRES-Cre::Ai14 mice underwent two cycles of either chronic intermittent ethanol (CIE) vapor exposure and chronic swim stress (CS) or control exposure. Whole-cell current-clamp electrophysiology was used to assess the intrinsic excitability of CRH-INs in L2/3 and 5/6 of the PL (n=14 mice), while a second cohort was processed for spatial transcriptomic

analysis (n=21 mice) using the standard Xenium Mouse Brain panel and 50 custom genes. Here we show PL CRH-INs exhibit opposing physiological adaptations to CIE+CS in L2/3 vs L5/6. L2/3 CRH-INs show a trend toward hyperexcitability and L5/6 CRH-INs show a trend toward hypoexcitability. Our transcriptomic data revealed high CRH-IN colocalization with vasoactive intestinal peptide (~75%) in L2/3 and somatostatin (~50%) in L5/6. Additionally, differential expression of many genes was observed in CRH-INs following CIE+CS, notably a global downregulation of many immediate early genes, a L2/3-specific upregulation of the GABAergic synaptic organizer Cbln4, and a L5/6-specific upregulation of the stress response modulator Crhbp. We also saw a global upregulation of the glucocorticoid effector Fkbp5. These findings suggest that PL CRH-INs comprise two distinct populations that respond differentially to chronic stress and alcohol both physiologically and transcriptomically. Because L2/3 and L5/6 INs gate distinct projections, layer-specificity of CRH-INs may translate to divergent behavioral outcomes. Therefore, further research is warranted to better understand, and ultimately mitigate, the behavioral consequences of these localized neuroadaptations.

Disclosures: G.P. Scheldrup: None. **L. LeMaster:** None. **C. Cooper:** None. **J. Crowley:** None. **Z. Hunter:** None. **S. Berto:** None. **J.A. Rinker:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.07/EE16

Topic: G.03. Stress and the Brain

Support: CAMH Discovery Fund

Title: Lipid peroxidation and PERK-eIF2α-mediated endoplasmic reticulum stress: Underlying mechanisms for chronic stress-induced vulnerability of prefrontal cortical somatostatin cells

Authors: *Y. WANG[1], M. MARCOTTE[2], E. SIBILLE[3], T. TOMODA[2], T. D. PREVOT[2]; [1]Univ. of Toronto, Toronto, ON, Canada; [2]Ctr. For Addiction and Mental Hlth., Toronto, ON, Canada; [3]CAMH - Univ. of Toronto, Toronto, ON, Canada

Abstract: Somatostatin-positive (SST^+) interneurons show cellular vulnerability in major depressive disorder (MDD), associated with reduced SST expression and impaired inhibitory function, as also observed in models of chronic stress. We previously demonstrated chronic stress-induced selective deregulation of the PERK-eIF2α branch of the endoplasmic reticulum (ER) stress response in SST^+ cells, contributing to reduced SST availability and behavioral emotionality. However, the upstream molecular events that shape this PERK-eIF2α deregulation remain poorly defined. Based on bioinformatic prioritization, we noted that proteostasis and lipid metabolism were two pathways significantly affected by chronic stress in SST^+ cells. Therefore, we hypothesize that chronic stress induces a state of lipid peroxidation in the ER and ER stress in SST^+ cells, triggering the observed SST^+ cell functional deficit and leading to symptom

emergence.Here, we used a unpredictable chronic mild stress (UCMS) model (0,1,3,5 weeks) in SST-GFP mice (N=4/group) to examine the temporal changes in levels of ER stress and lipid peroxidation in prefrontal cortex SST^+ interneurons. Behavioral assessment confirmed that 5-week UCMS induced increased emotionality and cognitive deficits. Immunofluorescence analysis on SST^+ cells (n = >50/condition) was then performed using an array of antibodies against ER stress markers (p-eIF2α, p-PERK), lipid peroxidation markers (MDA, 4-HNE, and 4-HHE) and the ER-resident enzymatic regulators of lipid metabolism (LPCAT3, PLA2G6).Upon UCMS exposure, we replicated a time-dependent increase in ER stress level and further observed a concurrent increase in lipid peroxidation in SST^+ interneurons, indicating progressive accumulation of oxidative lipid damage during chronic stress. In addition, we found a progressive increase in LPCAT3 and a decrease in PLA2G6, suggesting a chronic stress-induced imbalance in phospholipid remodeling that may alter oxidation-prone membrane lipid pools and hence increased lipid peroxidation burden.Integrating a bioinformatically-guided and time-resolved experimental framework, this study supports a model in which deregulated lipid metabolism and proteostasis deficits in the ER are key mediators of SST^+ interneuron vulnerability, and warrants further studies to decipher mechanistic links between lipid metabolism, lipid peroxidation and ER stress that may underlie SST^+ interneuron vulnerability to chronic stress.

Disclosures: Y. Wang: None. **M. Marcotte:** None. **E. Sibille:** None. **T. Tomoda:** None. **T.D. Prevot:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.08/EE17

Topic: G.03. Stress and the Brain

Support: NIH Grant PAR-24-152

Title: Investigating the role of alpha and beta adrenergic receptors on NF-κB-mediated transcription in the hippocampus

Authors: *C. BRYAN[1], B. CORBETT[2];
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Abstract: ABSTRACT
Objective: To determine whether pharmacologically inhibiting adrenergic receptors affects NF-κB levels and/or transcriptional activity. **Research Design:** Chronic Social Defeat Stress (CSDS) testing was conducted using retired breeder male CD1 mice (n=16) and C57BL/6 mice (n=24M:24F) aged 12-14 weeks to examine the expression of the pro-inflammatory transcription factor (NF-κB) in the hippocampus of male and female mice. To investigate the effects of chronic α1-AR and β-AR inhibition on NF-κB activation, male mice received the α1-AR

antagonist prazosin (n=24), the β-AR antagonist propranolol (n=24) or vehicle (n=24) via intraperitoneal injection, 60 min prior to daily defeat. Following α1-AR and β-AR inhibition, mice were tested with CSDS. Following CSDS, each group was observed in a social interaction (SI) test to assess sociability after chronic stress. Transcardial perfusion was performed 24h after SI, brains were collected and preserved for immunohistochemistry analysis. NF-κB-positive immunofluorescent images were quantified using confocal microscopy. **Results:** CSDS increased NF-κB activation in the granule cell layer (GCL) of the dentate gyrus in both male and female mice. Female mice have increased levels of NF-κB even in the absence of stress. Male mice treated with the α1-AR antagonist prazosin showed higher social interaction ratios after 10 days of CSDS than vehicle-treated mice. The β-AR blocker propranolol did not affect sociability. Inhibiting α1-AR and β-AR increases overall levels of NF-κB regardless of stress. **Conclusion:** This study confirms that female mice overall express higher levels of NF-κB compared to males. During chronic stress, NF-κB activation is increased in the GCL of the hippocampus. In stressed mice, prazosin increases sociability. This indicates that stress-induced activation of the alpha AR is responsible for reduced sociability following defeat.

Disclosures: C. Bryan: None. **B. Corbett:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.09/EE18

Topic: G.03. Stress and the Brain

Support: ES100221
AG000616

Title: Hippocampal area CA2 as a Hot Spot of Adrenal Hormone Signaling Revealed by Spatial Transcriptomics

Authors: B. KANDEMIR[1], J. M. WARD[1], D. CROTEAU[2], C. GU[1], G. M. ALEXANDER[1], N. BANSKOTA[2], E. LEHRMANN[2], S. DE[2], ***S. M. DUDEK**[1];
[1]NIH, Natl. Inst. of Envrn. Hlth. Sci., Research Triangle Park, NC; [2]Natl. Inst. On Aging, NIH, Baltimore, MD

Abstract: Glucocorticoids coordinate adaptive responses to stress, yet dysregulated glucocorticoid signaling is strongly linked to cognitive impairment, mood disorders and altered stress responsivity. In the brain, glucocorticoids signal through the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), ligand-activated transcription factors that translocate to the nucleus to regulate gene expression. Whereas GR is broadly expressed, MR is highly enriched in the hippocampus, particularly in area CA2, a subregion implicated in social behaviors like aggression. Conditional knock-out mouse studies demonstrate that MR regulates basal stress responsivity, learning, synaptic plasticity, and CA2-enriched genes such as *Amigo2* and *Fkbp5*.

However, whether endogenous glucocorticoids can shape transcriptional programs in CA2 remains unknown. We therefore asked whether corticosterone controls MR-associated gene expression in CA2 of male mice. Endogenous corticosterone was depleted by adrenalectomy (ADX; n=3) and compared with sham-operated and non-surgical controls (n=3, 6) 24 hours post-surgery. Immunofluorescence and immunoblot analyses from our lab and others has shown that ADX increased total MR protein and shifted MR toward the cytoplasm, indicating reduced receptor activation. In contrast, sham surgery increased nuclear MR relative to non-surgical controls, consistent with surgery-induced stress. To define transcriptional consequences of these glucocorticoid states, we performed spatial transcriptomics using the Visium HD platform. *Nr3c2* (encoding MR) expression was significantly elevated 2-fold in ADX mice, paralleling increased MR protein levels, whereas the CA2 marker *Amigo2* was reduced 4-fold in ADX and increased 3-fold in sham animals. Across conditions, corticosterone state similarly bidirectionally regulated 25 CA2-enriched genes, including the known glucocorticoid-responsive gene *Fkbp5*, predominantly being downregulated in ADX and upregulated in sham mice. Key findings were independently evaluated using the MERSCOPE imaging-based platform. These findings suggest that gene expression in CA2 is dynamically tuned by glucocorticoids, positioning this circuit as a candidate target in stress-related neuropsychiatric disease.This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author(s) are considered Works of the United States Government. The findings and conclusions presented in this abstract are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

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Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.10/EE19

Topic: G.03. Stress and the Brain

Title: Investigating the Role of Hippocampal δ-Subunit-Containing $GABA_A$ Receptors in Anxiety-Like Behavior in Adult Female Mice

Authors: *M. C. BROWN[1], N. MAMISASHVILI[2];
[1]Biol. Sci. s, [2]Fordham Univ., New York, NY

Abstract: Investigating the Role of Hippocampal δ-Subunit-Containing $GABA_A$ Receptors in Anxiety-Like Behavior in Adult Female Mice
Authors: Margot Brown, Dritjona Dule, Mohammad Abdullah, Nini Mamisashvili, Kaoutsar Nasrallah
Hormonal fluctuations across the ovarian cycle modulate brain physiology and may contribute to

sex differences in vulnerability to anxiety and mood disorders. Anxiety levels fluctuate throughout the estrous cycle, which is a recurring hormonal cycle, characterized by the sequential changes in the ovarian hormones, estrogen and progesterone and typically lasting 4-5 days in female rodents. However, how these fluctuations in estrogen and progesterone regulate neural activity and behavior remain incompletely understood. The hippocampus is a key brain structure in the regulation of anxiety. This medial-temporal lobe structure exerts inhibitory control over the hypothalamic-pituitary-adrenal (HPA) axis, thereby constraining the physiological stress response. However, whether and how tonic inhibition modulates the hippocampus' capacity to regulate the HPA axis remains largely underexplored. δ subunit-containing $GABA_A$ receptors (δ-$GABA_A$Rs) are particularly abundant in the dentate gyrus, main input area of the hippocampus. These receptors are highly sensitive to ambient GABA and are responsible for mediating tonic inhibition in the hippocampus. Moreover, levels of δ-GABAAR are modulated by the estrous cycle in female mice. However, their precise role in regulating anxiety, including across the estrous cycle, remain underexplored. We hypothesize that estrous-stage changes in δ-GABAAR-mediated inhibition are a key mechanistic driver that tunes hippocampal regulation of hypothalamic stress circuitry across the estrous cycle. To test this hypothesis, we used conditional removal of *Gabrd* from the hippocampus and assessed anxiety-like behaviors across the estrous cycle in adult female mice. This work may reveal novel mechanisms underlying the regulation of anxiety-like behavior across the estrous cycle, with implications for neuropsychiatric disorders such as premenstrual syndrome (PMS), thus highlighting hippocampal δ-$GABA_A$Rs as a potential therapeutic target for such disorders.

Disclosures: M.C. Brown: None. **N. Mamisashvili:** None.

Poster

PSTR064: Stress: Cellular Actions

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR064.11/EE20

Topic: G.03. Stress and the Brain

Support: 5 R01 NS132778
TST TL1 TL1TR002647
American Heart Association 916018 co-funded by the Voelker Fund
Veteran's Administration CDA2
5T32NS082145-12
Owens Foundation

Title: LRP1 dependent modulation of NMDA receptors in neurogenesis

Authors: *N. MARION[1], K. DIETERT[2], P. REED[1], S. SPRAGUE[3], E. KOKOVAY[4], N. L. SAYRE[5];
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of Cell. and Structural Biol., UT Hlth. Sci. Ctr. At San Antonio, San Antonio, TX; [5]Neurosurg., UT Hlth. Sci. Center, San Antonio, San Antonio, TX

Abstract: Adult hippocampal neurogenesis (AHN) is important in regulating response to stress, memory, and emotion. However, the mechanisms driving long-term cognitive and behavioral deficits following stress are poorly understood. Stress increases NMDA receptor activation and alters localization. Interestingly, the GluN2B subunit shifts from synaptic to extrasynaptic localization as neurons mature. GluN2B activation is also associated with promoting cell death. Whether GluN2B localization could drive increases in stress induced cell death in adult-born neurons is unknown but suggests a possible mechanism which could explain stress-dependent induction of cell death in the hippocampus. Low-density lipoprotein receptor-related protein 1 (LRP1) is a protein of interest given its role in AHN and internalization of the GluN2B subunit. We propose by understanding this mechanism we can improve our pathobiological understanding of stress related psychiatric disorders and advance treatment. Our laboratory identified LRP1 as a novel modulator of AHN. Using inducible Nestin-Cre, we selectively targeted LRP1 knockout (KO) in adult neural stem cells (NSC) of 3 month old floxed mice, while using age-match Nestin-Cre control mice that lacked floxed LRP1. KO mice exhibited elevated anxiety-like behavior and Barnes maze revealed impaired hippocampal memory compared to controls at 10 months. Histology revealed an increase in NeuN-positive neurons in 10 month LRP1 KO mice, indicating potential disruption of hippocampal neural circuitry. Given the increase in mature NSCs, we analyzed the number of apoptotic NSCs. Our data revealed a decrease in TUNEL-positive cells in 4 month LRP1 KO mice but only in mice that had spent time on the elevated plus maze, suggesting impaired apoptosis due to acute stress may underlie the observed increase of mature neurons. We also examined changes in proliferation between groups via flow cytometry and found LRP1KO mice had increased proliferation compared to controls, indicating increases in proliferation could also contribute to the increase in mature neurons. Last, using expansion microscopy we are examining the localization of the GluN2B subunit in LRP1KO mice after stress and expect to observe mislocalization of the GluN2B subunit in the synapse. Future work will investigate how apoptosis is altered in LRP1KO mice following acute stress and analyze how both stress and LRP1KO alter NMDA receptor localization. Ultimately, our goal is to determine whether LRP1 in adult-born NSCs plays a role in stress-related psychiatric disorders by examining stress-induced cellular responses, as well as elucidating the underlying molecular mechanisms.

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Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.01/EE21

Topic: G.03. Stress and the Brain

Support: PSC-CUNY Cycle 56 ENH 56-191
PSC-CUNY Cycle 55 TRADB-55-287

Title: Resting Heart Rate Moderates the Association Between PM2.5 Exposure and Anxiety Symptoms in Adolescents

Authors: *M. BLUM[1,4], M. BALDYGA[4], A. MAHMOOD[4], D. HASSOUNEH[4], A. LAVI[5,4], I. KHAN[4], K. VEMU[4], N. MIZUTANI[4], Y. NOMURA[4,6,7,2,3];
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Abstract: Background: Air pollution has been associated with adverse mental health outcomes during adolescence, a developmental period marked by increased vulnerability to anxiety and mood disorders. Autonomic nervous system functioning may influence susceptibility to environmental stressors, but its role in modifying associations between air pollution exposure and emotional well-being remains poorly understood.
Objective: The current study examines the independent and joint associations between fine particulate matter (PM2.5), resting heart rate, and momentary anxiety and depressive symptoms in adolescents.
Methods: Data were collected during Winter 2026 from a subset of the Stress in Pregnancy Study, a longitudinal birth cohort in New York City (N = 30, 50% female, ages 10-15 years old). Participants completed ecological momentary assessment surveys three times daily to report their emotional states on a 7-point Likert scale, from which composite anxiety and depression scores were derived (N = 377 surveys). PM2.5 exposure estimates were obtained from the OpenWeatherMap database using smartphone-derived GPS locations within a 3-hour window surrounding survey completion. Resting heart rate was measured using a Fitbit Charge 6 smartwatch during the longest sleep period within the 24 hours preceding each survey. Generalized estimating equations were used to examine main and interaction effects of standardized PM2.5 exposure and resting heart rate on anxiety and depression scores, accounting for repeated measures and adjusting for age, sex, and indoor/outdoor status at the time of survey completion.
Results: PM2.5 exposure and resting heart rate were not independently associated with anxiety or depression scores. However, resting heart rate significantly modified the association between PM2.5 exposure and anxiety symptoms ($\beta = 0.045$; 95% CI 0.021, 0.070; $p < .001$), such that higher PM2.5 exposure was associated with greater anxiety symptoms among adolescents with higher resting heart rates. No significant interaction was observed for depression symptoms.
Conclusions: These findings suggest that resting heart rate may identify adolescents who are more susceptible to the emotional impacts of air pollution exposure. Incorporating physiological indicators of autonomic functioning into environmental mental health research may improve understanding of individual differences in vulnerability to environmental stressors. Larger studies are needed to confirm these findings and identify adolescents at greatest risk for pollution-related emotional distress.

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Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.02/EE22

Topic: G.03. Stress and the Brain

Support: 3R01MH136102-01S1
1R01MH136102-01

Title: Distinct Modulation of Limbic Activation by Autonomic and Endocrine Stress Response Systems in Adolescents

Authors: *M.-Y. CHU, A. BELGER;
Dept. of Psychiatry, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Stress is a major contributor to the development and persistence of mental disorders. Adolescence is a developmental period characterized by puberty and social transitions, which may increase vulnerability to the long-term effects of stress on mental health. How hormonal stress responses are translated into limbic brain activation is shaped by Respiratory Sinus Arrhythmia (RSA), an indicator of autonomic regulatory capacity. However, the modulatory role of RSA in HPA axis-brain coupling during adolescence and its association with the severity of depressive symptoms remains poorly understood. We examined the association of RSA responsivity and cortisol increase during the Trier Social Stress Test with limbic activation of amygdala and hippocampus during the Montreal Imaging Stress Task in 47 adolescents (33F, 14M; mean age=14.28 years, range=13-15.67, SD=0.71) experiencing a range of depressive symptom severity. Linear mixed models were used, controlling for age, sex, hemisphere, and saliva sampling time. Significant three-way interactions were found for cortisol Area Under the Curve to increase (AUCi) × RSA × hemisphere and cortisol AUCi × depressive symptom severity × hemisphere. Under control conditions, both RSA and depressive symptom severity modulated the cortisol AUCi-limbic activation relationship. Under stress conditions, the effect of depression severity disappeared, whereas RSA modulation remained. RSA showed region-specific modulation effects: In the amygdala, the modulating effect of recovery RSA was stronger than that of reactivity RSA. Moreover, this effect was stronger in the left amygdala during the control condition ($\beta = 0.11$, $p = .007$) but stronger in the right amygdala during the stress condition ($\beta = 0.18$, $p = .062$). This reverse hemispheric lateralization pattern suggests that recovery RSA is more closely linked to parasympathetic recovery processes in the amygdala, with the stress-related auditory feedback increased right-hemisphere involvement under stress. In contrast, in the hippocampus, the modulating effect of reactivity RSA was stronger than that of recovery RSA. This effect was consistently stronger in the left hippocampus across both control ($\beta = -0.08$, $p = .012$) and stress conditions ($\beta = -0.14$, $p = .012$), suggesting that reactivity RSA

may be more relevant to immediate stress responding and contextual processing. These findings suggest that individual differences in RSA are a robust predictor of stress-related brain-body coupling during adolescence, with the recovery and reactivity components affecting distinct regulatory processes across the amygdala and hippocampus.

Disclosures: M. Chu: None. **A. Belger:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.03/EE23

Topic: G.03. Stress and the Brain

Support: the STI2030-Major Projects (no. 2022ZD0212900)
National Natural Science Foundation of China (nos. 82471533 and 32071058)

Title: A brain-heart sympathetic axis couples affective behavioral state and cardiovascular responses

Authors: *Y. HAN[1], L. LU[2], J. SHI[3];
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Abstract: Chronic psychological stress and negative emotion are critical drivers of cardiovascular diseases, yet the specific pathways that link affective behavioral state to maladaptive cardiovascular responses have largely remained unclear. Here, we discover a polysynaptic, top-down circuit that commands sympathetic outflow to the heart, thus driving concurrent emotional and cardiovascular pathologies. Combining virus-based tracing and mapping, we identified the ventral bed nucleus of the stria terminalis (vBNST) as a GABAergic relay that transmits prelimbic cortex (PL)-derived stress signals to the paraventricular nucleus of the hypothalamus (PVN). We also observed decreased activity in both the PL^{Glu}→vBNST and $vBNST^{GABA}$→PVN circuits after chronic stress. Chemogenetic activation of the tri-synaptic PL→vBNST→PVN pathway not only rescued chronic stress-induced anxiety-like behaviors but also normalized cardiovascular dysfunction, as indexed by tachycardia and elevated blood pressure. Moreover, The PVN corticotropin-releasing hormone neurons serves as a key node converting these central signals into peripheral sympathetic output. Pharmacological ablation or surgical removal of cardiac sympathetic innervation abolished this polysynaptic circuit-mediated modulation of cardiovascular activity, further confirming the sympathetic effector pathway. Taken together, our findings reveal a brain-heart axis that integrates emotional processing with cardiovascular pathology, providing a precise circuit-level mechanism and potential targets for treating stress-related psychosomatic disorders.

Disclosures: Y. Han: None. **L. Lu:** None. **J. Shi:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

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Program #/Poster #: PSTR065.04/Web Only

Topic: G.03. Stress and the Brain

Support: NIH grant R01NS132772-01A1 (YX, LZ)

Title: Therapeutic effects of N-acetyl-seryl-aspartyl-lysyl-proline on functional recovery after traumatic brain injury in female rats: a study of therapeutic window and treatment duration

Authors: *X. WANG[1], H. PANG[1], M. CHOPP[2], Y. ZHANG[4], L. CHEN[5], Z. ZHANG[6], L. ZHANG[3], Y. XIONG[4];
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Abstract: Background: Previous study identified AcSDKP initiated 1 h at 0.8 mg/kg/day as the optimal dose for improving functional recovery after TBI in rats. This study investigated the therapeutic window and treatment duration of AcSDKP in rats following TBI. **Methods:** Young female Wistar rats were assigned to a therapeutic window study or a treatment duration study (n = 8/group). In the window study, AcSDKP (0.8 mg/kg/day) treatment was initiated at 1, 2, 6, 24, or 72 h after CCI-induced TBI and continued for 3 days. In the duration study, treatment was initiated 1 h after TBI and continued for 3, 7, or 14 days. AcSDKP or Vehicle was delivered subcutaneously via osmotic pumps. Cognitive, sensorimotor and neurological outcomes were assessed using the foot-fault test, adhesive removal test, mNSS, and Morris water maze (MWM). Brains were collected at for lesion volume, immunohistochemical analyses of neuroinflammation (CD68 and GFAP staining) and neuronal loss (NeuN staining). **Results:** In the therapeutic window study, AcSDKP initiated at1 to 72 h post-injury significantly improved sensorimotor function, as evidenced by reduced foot-fault frequency and shorter adhesive removal times compared with vehicle group rats. Treatment initiated at 1 h post-injury produced the greatest neurological improvement, significantly reducing mNSS scores and enhancing cognitive performance in the MWM, as indicated by decreased latency to locate the hidden platform and increased % time spent in the target quadrant. In the duration study, AcSDKP treatment initiated 1 h after TBI and continued for 3, 7, or 14 days significantly improved sensorimotor and neurological outcomes. Overall, only the 1 h initiation group exhibited significant improvements in spatial learning and memory. Functional recovery was accompanied by reduced lesion volume, increased NeuN-positive neuronal density, decreased CD68-positive microglial/macrophage activation, and reduced GFAP-positive astrocyte reactivity. Both studies, AcSDKP treatment initiated at 1 h post-injury consistently produced the most robust behavioral and histological benefits. **Conclusions**: AcSDKP confers significant neurobehavioral and histological benefits after TBI in female rats, with efficacy influenced by treatment initiation time and duration. Treatment initiated at 1 h post-injury consistently produced the most robust functional recovery, neuronal preservation, and attenuation of neuroinflammatory responses,

defining an optimal therapeutic window for AcSDKP administration. These findings provide important preclinical evidence supporting the continued development of AcSDKP as a therapeutic candidate for TBI.

Disclosures: X. Wang: None. **H. Pang:** None. **M. Chopp:** None. **Y. Zhang:** None. **L. Chen:** None. **Z. Zhang:** None. **L. Zhang:** None. **Y. Xiong:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.05/EE24

Topic: G.03. Stress and the Brain

Support: Wisconsin Partnership Program at the University of Wisconsin School of Medicine and Public Health

Title: Gonadotropin-releasing hormone agonist alters the predator odor induced depressive-like behaviors in juvenile female rats

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Abstract: Gonadotropin-releasing hormone agonists (GnRHa), also known as puberty blockers, act to suppress puberty in transgender and nonbinary adolescents, a time that also coincides with increased vulnerability to mental health risk. Therefore, it is important to understand the impact of pausing puberty on brain and behavior during postpubertal development. Previously, we examined the impact of leuprolide acetate (LA), a GnRHa, on anxiety-related behaviors in juvenile rats and found that LA significantly attenuates anxiety-like behaviors in adolescent rats. Upon finding these changes, we wished to determine how treatment of GnRHa would blunt predator odor induced stress. Therefore, we treated juvenile female rats with LA or control from P27-P41. Subjects were concurrently exposed to predator odor or control between P34-P35. Following predator odor exposure, animals underwent testing for anxiety-like behavior using the elevated zero maze (P40) and depressive-like behaviors using the forced swim task (P41). We found that treatment of LA decreased anxiety-like behaviors overall, but not predator odor induced anxiety. However, LA decreased depressive-like behaviors induced by predator odor as measured by the forced swim task. Our findings suggest that GnRH action plays a critical role in modulating stress response during adolescent development.

Disclosures: A. Nguyen: None. **A.K. Johnson:** None. **A.P. Auger:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.06/EE25

Topic: G.03. Stress and the Brain

Support: CAPES/CNPQ Research, Brazil

Title: E-Cigarette Exposure Disrupts Neurobehavioral Function and Conserved Molecular Stress Responses: An in vivo Integrative Analysis of Drosophila and Human Transcriptomic Datasets.

Authors: *T. A. OTENAIKE[1], J. TEIXEIRA ROCHA[2], E. L. LORETO[1];
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Abstract: Electronic cigarettes are widely marketed as safer alternatives to conventional tobacco products; however, their intrinsic biological, systemic, and neurobehavioral effects remain incompletely characterized. Thus, this study investigated whether e-liquid exposure elicits behavioral changes and toxicity through oxidative, metabolic, and neurotoxic mechanisms and disrupts behavior and cellular homeostasis. To test these, we combined in vivo toxicological assessment in *Drosophila melanogaster* with transcriptomic reanalysis and network-based systems biology approaches. Adult *Drosophila melanogaster* (Oregon R strain; males and females) were exposed to 0.06, 0.08, and 0.12 mg/mL E-liquid. Survival, developmental, locomotion, body weight, total protein content, acetylcholinesterase (AChE), monoamine oxidase (MAO), superoxide dismutase (SOD), glutathione-S-transferase (GST), catalase (CAT), reduced glutathione (GSH), heat shock protein gene expression (HSP70 and HSP83), sleep behavior, and olfactory associative memory were evaluated. Chemical constituents of the e-liquid were characterized by GC-MS and GC-FID. Differential gene expression analyses were performed using publicly available *Drosophila* head transcriptomic data (GSE35930) and human transcriptomic datasets (GSE185538 and GSE278792). Network pharmacology, protein-protein interaction analyses, and molecular docking were employed to identify candidate molecular targets and pathways. E-liquid exposure significantly reduced survival, impaired locomotor performance, decreased body weight and protein content, altered cholinergic and monoaminergic enzyme activities, disrupted antioxidant defenses, increased HSP70 and HSP83 expression, impaired sleep activity, and reduced associative memory performance. Transcriptomic analyses revealed deregulation of genes associated with nicotinic receptor signaling, oxidative stress responses, inflammatory pathways, cellular stress adaptation, and apoptosis in both *Drosophila* and human datasets. Network analyses identified AKT1, CHRNA7, NFKB, etc. as central hub nodes within conserved stress-response networks. Molecular docking predicted favorable nicotine interactions with these targets, supporting their potential involvement in nicotine-associated cellular responses. Therefore, these findings suggest that e-liquid exposure induces neurobehavioral dysfunction and molecular stress responses, and the integration of in vivo neurobehavioral, toxicology, comparative transcriptomics, and network pharmacology provides candidate pathways for future neurotoxicological investigation.

Disclosures: T.A. Otenaike: None. **J. Teixeira Rocha:** None. **E.L. Loreto:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.07/EE26

Topic: G.03. Stress and the Brain

Support: P50 NIAAA #AA022534

Title: Prenatal alcohol exposure (PAE) and mild adolescent stress induce anxiety-like behavior following mild adult stress in mice

Authors: *J. ZIMMERLY[1], E. NAKHLA[1], C. TOMICEK[1], N. CASTRO[1], A. K. FERNANDEZ-OROPEZA[2], S. DAVIES[3], J. MAXWELL[5], D. N. LINSENBARDT[3], C. F. VALENZUELA[6], E. D. MILLIGAN[4];
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Abstract: Prenatal alcohol exposure (PAE) results in fetal alcohol spectrum disorder (FASD). Mouse models of FASD show greater anxiety responses to stress and increased expression of cytokines and chemokines in brain and peripheral tissues. Adolescence is a critical period which includes refinement of limbic structures important for mood regulation that underlie stress-responsive programming engaged in adulthood. Acute adolescent social isolation in mice is a potent perceived stressor during this vulnerable period and is linked to adult anxiety. Production of proinflammatory cytokines (interleukin-1β, IL-1β) and chemokines (CXCL1) in limbic regions is linked to anxiety-like behaviors. We hypothesized that PAE creates further vulnerabilities to the adolescent stress-response programming resulting in adult anxiety-like behavior and increased cytokine/chemokine expression in limbic regions in response to mild adult stress. Male and female offspring with PAE or prenatal water exposure (controls) were divided into the following: (1) home cage controls (HCC), adolescent (PND 39-44) mice (2) exposed to a 1hr isolation stress for three consecutive days without subsequent adult stress, or (3) with subsequent adult stress (4) adult mice (PND 95) exposed to a 30-min restraint stress without prior adolescent isolation stress. All adult mice were placed in the elevated plus maze (EPM; 5 min) followed by assessment in the activity monitoring system to identify anxiety-like behaviors. Blood plasma levels of the stress hormone corticosterone (CORT) were assessed following tail vein nick from HCC or immediately after both adolescent and adult stress via enzyme-linked immunosorbent assay (ELISA). Protein from adult prefrontal cortex and hippocampus was assayed using the meso-scale-discovery (MSD) multiplex immunoassay to quantify levels of proinflammatory cytokines/chemokines. Compared to HCCs, elevated CORT levels were observed from adolescent and/or adult mice following stress. All mice with prior adolescent stress demonstrated decreased exploratory behavior. Adult PAE males with adolescent stress and subsequent adult stress spent more time in the closed arms and less time in the open arms of the EPM compared to HCC mice. PAE increased hippocampal CXCL1 and IL-1β from males and

females with adolescent stress *and* adult stress. Ongoing studies are examining the impact of PAE and stress on adult cytokine levels in the hypothalamus and chemokine levels from peripheral immune organs. These data support that PAE dysregulates the adult behavioral response to stress in adolescence and adulthood, leading to development of anxiety-like behaviors.

Disclosures: J. Zimmerly: None. **E. Nakhla:** None. **C. Tomicek:** None. **N. Castro:** None. **A.K. Fernandez-Oropeza:** None. **S. Davies:** None. **J. Maxwell:** None. **D.N. Linsenbardt:** None. **C.F. Valenzuela:** None. **E.D. Milligan:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.08/EE27

Topic: G.03. Stress and the Brain

Support: UBACYT 20020190100222BA (Universidad de Buenos Aires)
PICT-I-A-00918 (FONCYT)
Florencio Fiorini Fundation 2024 grant

Title: Hippocampus-dependent behavioral alterations induced by early febrile seizures and traffic noise exposure: modulatory effects of environmental enrichment

Authors: *G. N. CORSI[1], D. BROGGI[2], A. ROSSI[3], L. R. GUELMAN[2,4], L. D´ALESSIO[3,4], S. J. MOLINA[2];
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Abstract: Febrile seizures (FS) are a common neurological event during childhood and are generally considered benign. However, prolonged FS can induce long-term cognitive and behavioral alterations, hippocampal (HC) damage, and increase the risk of developing temporal lobe epilepsy. The developing HC is particularly vulnerable to environmental factors, including adverse stimuli such as urban traffic noise and beneficial interventions such as environmental enrichment (EE). To date, the effects of adolescent traffic noise exposure as a second environmental challenge in subjects that experienced FS early in life have not been investigated, nor has the potential of EE to protect against such effects. Therefore, this study aimed to evaluate the impact of FS and adolescent traffic noise exposure on HC- related behaviors and to

investigate whether EE could prevent these alterations.Male Wistar rats were subjected to hyperthermia (HT; 41 °C for 30 min) on postnatal day (PD) 10. After weaning, animals were housed under either standard or EE conditions. At PD28, they were exposed to traffic noise (2 h/day for 5 days). HC-related behaviors were assessed using the open field, inhibitory avoidance, and elevated plus maze tasks.A pronounced impairment in associative memory was observed in rats subjected to HT regardless of housing or noise exposure conditions. In contrast, habituation memory was enhanced by either HT or traffic noise exposure alone, whereas no such effect was observed when these stimuli were combined or when animals were housed under EE conditions. Interestingly, the behavioral effects of traffic noise were not additive to those induced by early-life HT. EE, either alone or in combination with noise or HT, reduced anxiety-like and risk-assessment behaviors. Additionally, EE increased vertical exploratory activity and decreased horizontal locomotor activity, regardless of the other experimental conditions.These findings suggest that FS differentially affected HC-related memories and that the neuroprotective effects of EE depended on the behavioral domain evaluated. EE prevented changes in habituation memory but failed to reverse associative memory deficits, suggesting that its efficacy may be greater when behavioral alterations are less severe. Moreover, EE promoted exploration and exerted anxiolytic effects. However, animals housed in EE also exhibited reduced caution in potentially threatening environments, which may increase their exposure to risk. Overall, adolescent traffic noise exposure and early-life FS produced distinct behavioral effects, while EE exerted both protective and modulatory influences on HC-related behaviors.

Disclosures: G.N. Corsi: None. **D. Broggi:** None. **A. Rossi:** None. **L.R. Guelman:** None. **L. D´Alessio:** None. **S.J. Molina:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.09/EE28

Topic: G.03. Stress and the Brain

Title: Maternal High-Fat Diet Shapes Adolescent Social Behavior in Melanocortin-3 Receptor-Deficient Offspring

Authors: *F. HOSSAIN[1], C. P. BASTOS[1], M. HOCHSTETLER[3], A. DODGE[1], S. MALLICK[1], A. JEFFERS[1], S. MITRA[2];
[2]Biomed. Sci., [1]Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK; [3]New York Univ., New York, NY

Abstract: Maternal metabolic state and melanocortin signaling critically influence energy homeostasis, yet their combined consequences on behavioral outcomes during adolescence, a critical window for establishing long-term neurobehavioral trajectories, remain majorly understudied. Using a maternal preconception high-fat diet (HFD), we conducted a comprehensive behavioral battery assessing locomotor activity, anxiety-like behavior,

recognition memory, social preference, and thermal sensitivity in adolescent melanocortin-3 receptor (MC3R) knockout (KO) offspring. Among these domains, our most significant findings emerged specifically in social preference. We found that female KO offspring exhibited significantly reduced sociability following preconception HFD, whereas male KO offspring were unaffected. These findings identify a previously unrecognized vulnerability of adolescent social development to maternal metabolic challenges in the absence of MC3R signaling.

Disclosures: F. Hossain: None. **C.P. Bastos:** None. **M. Hochstetler:** None. **A. Dodge:** None. **S. Mallick:** None. **A. Jeffers:** None. **S. Mitra:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.10/EE29

Topic: G.03. Stress and the Brain

Title: Adolescent binge eating induces maladaptive behaviors that are sex-dependently attenuated by ketamine

Authors: *A. BARKLEY[1], P. REZAIE BOROON[2], S. BATES[3];
[1]Psychology, California State University, Chico, Chico, CA; [2]UC San Diego, San Diego, CA; [3]Psychology, CSU Chico, Chico, CA

Abstract: Binge-eating disorder (BED) is the most prevalent eating disorder in the United States and is frequently comorbid with substance use and anxiety disorders. BED is characterized by chronic overeating accompanied by a loss of control during binge episodes and commonly emerges during adolescence. However, few preclinical studies have examined the behavioral outcomes of BED during this critical developmental period and there is currently only one FDA approved treatment for BED. Ketamine, a dissociative anesthetic used to treat Major Depressive Disorder, has shown limited but promising effects in reducing BED symptomatology. However, its effects have not been evaluated in a rodent model of binge eating. Mice were given an assigned diet for 2 hours a day, standard chow or a high-fat diet, three times a week for four weeks. Twenty-four hours before the first binge session each week, ketamine or saline was administered. Following the binge eating cycle, a six day Conditioned Place Preference (CPP) paradigm was conducted to measure morphine reward. To test the level of anxiety, the mice underwent an Elevated Plus Maze (EPM) test 24 hours after the final day of CPP. Finally, morphine withdrawal was assessed by administering naloxone and recording withdrawal symptoms for 30 minutes. Intermittent, limited-access to a high-fat diet successfully induced a binge-like phenotype, characterized by escalation of palatable food intake. Although ketamine pretreatment did not significantly reduce binge-like consumption overall, a significant amount of ketamine-treated mice failed to develop a binge-like phenotype. Binge-eating males displayed heightened morphine withdrawal-like behaviors, whereas no consistent effects of binge eating or ketamine were observed on morphine reward. On the EPM, male and female binge-eating groups

exhibited increased impulsive-like behavior. Notably, ketamine produced sex-dependent behavioral effects, reducing impulsivity in males while increasing impulsivity in females. Overall, these findings suggest binge eating may alter impulsivity and response to morphine in a sex-dependent manner. Although binge eating did not significantly modify morphine reward in this model, it increased impulsivity-like behavior in both males and females and enhanced withdrawal-related responses in males, supporting overlap between binge-eating and substance-use-related phenotypes. Importantly, ketamine's behavioral effects differed by sex, underscoring the need to consider biological sex when evaluating pharmacological interventions for binge-eating behaviors.

Disclosures: A. Barkley: None. **P. Rezaie Boroon:** None. **S. Bates:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.11/EE30

Topic: G.03. Stress and the Brain

Title: The Long-Term Effects of Chronic Stress and Binge Eating in Adolescence

Authors: S. SKAGGS[1], P. REZAIE BOROON[2], *S. BATES[1];
[1]CSU Chico, Chico, CA; [2]UC San Diego, San Diego, CA

Abstract: Binge eating disorder (BED) is the most prevalent eating disorder in the United States. Stress, anxiety, and depressive disorders are frequently comorbid with BED and can produce long-lasting changes in behavior and reward processing. We hypothesized that chronic stress and exposure to a high-fat diet (HFD) would independently alter affective and reward-related behaviors, but combined exposure would produce the most pronounced changes across measures of anxiety, depression, and cocaine-seeking behavior, with the greatest vulnerability shown in female mice. To test this, adolescent C57BL/6 mice received intermittent access to either standard chow or a HFD of Reese's Peanut Butter chips every other day for 2-hours, across 12 total sessions beginning on post-natal day (PND) 39. To model chronic stress, mice were exposed to the Single Prolonged Stress (SPS) procedure prior to the first dietary session (PND 38), which involved a battery of stressors. The day after the final dietary session, the mice underwent consecutive behavioral tests from PND 62 to PND 69, consisting of the Elevated Plus Maze, Novelty Suppressed Feeding, Splash Test, and a 4-day Conditioned Place Preference (CPP) procedure to measure the effects of diet and stress on the rewarding properties of cocaine versus saline. Our preliminary data suggest that stressed male mice exposed to an HFD consume more food across sessions than those on standard chow, whereas stressed female mice exposed to an HFD exhibit greater anxiety-like and reward-seeking behaviors in the CPP paradigm. Overall, our findings have suggested sex-dependent differences in maladaptive behaviors in response to combined high-fat diet and chronic stress exposure. Future research will include molecular analyses using quantitative polymerase chain reaction (qPCR) to examine opioid and adrenergic

gene expression in the prefrontal cortex and striatum. Combining behavioral and molecular analyses will allow for greater insight into the underlying mechanisms involved in the stress response and the potential moderation of reward and emotional processing. These findings will contribute to the growing body of research exploring the intersection of chronic stress and BED during adolescence, and may inform more targeted, sex-specific treatment approaches for stress-related development of eating disorders.

Disclosures: S. Skaggs: None. **P. Rezaie Boroon:** None. **S. Bates:** A. Employment/Salary (full or part-time):; CSU Chico.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.12/EE31

Topic: G.03. Stress and the Brain

Support: Faculty Grant from Barnard College

Title: Pubertal development and prior stress experience interact to shape hormonal and central stress reactivity in male and female rats

Authors: *R. D. ROMEO, S. CRUZ, J. ORTIZ, R. RAO;
Barnard Col., New York, NY

Abstract: Puberty is marked by many gains in physiological and neurobehavioral function. Yet, it is also a time when many stress-related vulnerabilities emerge, such as mood and metabolic disorders. There are pubertal differences in stress-induced hypothalamic-pituitary-adrenal (HPA) axis responses, which may contribute to these vulnerabilities. Previous studies have shown that prepubertal male and female rats show more prolonged stress-induced hormonal responses compared to their adult counterparts. Experience with stressors further shapes these pubertal changes in hormonal stress reactivity, such that adult males exposed to repeated restraint stress display a habituated hormonal response while prepuberal males do not. Although adult females show habituation to repeated stress, it takes them greater exposures to display this habituation compared to adult males. It is currently unknown whether prepubertal females show changes in hormonal reactivity following repeated restraint. Moreover, it is unclear what neural substrates may mediate these age-, sex-, and experience-dependent changes in reactivity. Thus, we exposed prepuberal (30 days of age, d) and adult (70d), male and female rats to either a single 30min restraint stress (1RS) or a single 30min restraint on four consecutive days (4RS; n=6 per group). Plasma corticosterone and c-Fos-positive cells were quantified in the paraventricular nucleus of the hypothalamus (PVN) and posterior paraventricular nucleus of the thalamus (pPVT). In males, we replicated previous data, such that we found a prolonged hormonal response in 30d males compared to 70d males following 1RS, and only 70d males showed hormonal habitation in response to 4RS. Cellular activity in the PVN was higher in 30d compared to 70d males in

response to 1RS and 4RS, while responses in the pPVT were elevated in 30d males, but only under basal conditions following 4RS. Though 70d females showed a higher peak hormonal response and a faster return to baseline compared to 30d females, hormonal reactivity at both ages was similar in response to 1RS and 4RS, suggesting that females do not habituate to 4RS. Activity patterns of the PVN and pPVT were also similar across both stress experiences, and like 30d males, 30d females showed elevated c-Fos in the pPVT under basal conditions after 4RS. These data indicate that puberty and prior stress experience shape hormonal and central stress reactivity in both males and females. However, additional research is needed to more fully understand the mechanisms that mediate how puberty, stress, and sex interact to modulate HPA function, and ultimately how these factors contribute to stress-related dysfunctions.

Disclosures: R.D. Romeo: None. **S. Cruz:** None. **J. Ortiz:** None. **R. Rao:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.13/EE32

Topic: G.03. Stress and the Brain

Support: Student Award for Research and Creativity, CSU Chico

Title: Are you feeling what I'm feeling? The effects of social environment and stress in adolescent mice

Authors: *A. SINGELIS[1], S. BATES[2];
[1]California State University, Chico, Chico, CA; [2]Psychology, CSU Chico, Chico, CA

Abstract: Across an individual's life, the factor that exerts one of the strongest influences on their experience is their social environment. Adolescents spend a great deal of time influencing one another, forming cliques, and mutually guiding each other's development. Social environment can have a positive or negative influence on one's overall development. Here, we will seek to understand if stress produces a similar phenomenon, by examining whether the presence of non-stressed mice buffers stress-related behaviors and neural changes in those that are stressed, and if stress-related behaviors and neural changes transfer to non-stressed mice. Our study will test the effects of mixed vs unmixed stress housing conditions on stress' adverse effects in adolescence. Our previous study found that stress increased depression-like behavior in adolescent male mice, and increased anxiety-like behavior in adolescent female mice. We hypothesize that *(1)* mixed housing conditions will buffer stress-related behavioral and neuronal changes in stressed mice, *(2)* that mixed housing conditions will increase stress-related behavioral and neuronal changes in stress-naïve mice, and *(3)* that these social effects will be greater in female mice. Adolescent C57BL/6J mice housed in groups of four will be randomly assigned to one of four conditions on postnatal day 44: stress unmixed, stress mixed, stress-naïve mixed, and stress-naïve unmixed. Stressed mice will be subject to a battery of stressors we have

used previously to produce a stressed behavioral phenotype. Then, mice will be tested on the sucrose preference test to measure depression-like behavior, the elevated plus maze to measure anxiety-like behavior, the morphine locomotor test to measure opioid vulnerability, and the social interaction test to measure social reward. Finally, we will use immunohistochemistry to quantify stress hormone receptors in brain regions such as the locus coeruleus, hippocampus, and prefrontal cortex. Stress produces adverse effects on neural development. Our study seeks to investigate the extent to which stress-related behavioral and neural changes can be socially transferred and buffered and examine underlying neural mechanisms of this effect. This will improve understanding of how adolescents with differing stress levels influence and are influenced by those around them. Particularly as adolescents form tight-knit social groups and spend extensive periods of time together, quantifying stress transference and buffering effects are vital to improving adolescent mental health.

Disclosures: A. Singelis: None. **S. Bates:** A. Employment/Salary (full or part-time):; California State University, Chico.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.14/FF1

Topic: G.03. Stress and the Brain

Support: College of Arts and Sciences

Title: Chronic Unpredictable Stress Produces Persistent Hippocampal-Prefrontal Circuit Dysfunction and Alters Fear Memory Reactivation in Female Rats

Authors: *N. SYME, C. CHARPENTIER, S. AZERRAD, M. MARCILLE, P. SACK, T. PANTALENA, A. J. BETZ;
Quinnipiac Univ., Hamden, CT

Abstract: Female rodents remain underrepresented in preclinical stress research despite the disproportionate burden of stress-related disorders in women. To examine the long-term consequences of adolescent stress exposure, female rats housed in groups of six were subjected to a 26-day chronic unpredictable stress (CUS) paradigm beginning on PND39 consisting of two randomized daily stressors, including periods of social isolation. During adolescence, CUS-exposed animals exhibited reduced weight gain and increased locomotor activity, indicating persistent physiological and behavioral effects of stress exposure. However, anxiety-like and depressive-like behaviors were not detected on the elevated plus maze or forced swim test. To determine whether adolescent stress produces enduring alterations in memory function, the same cohort was evaluated approximately one year later using a two-day trace fear conditioning (TFC) procedure. CUS animals exhibited intact fear acquisition during training, indicating preserved associative learning. In contrast, memory retrieval was impaired on the subsequent test day, with

reduced baseline freezing and freezing during tone presentation, indicating impaired later expression or retrieval. To further assess memory stability, animals underwent reactivation sessions following an extended post-conditioning interval. During the initial reactivation session, CUS animals displayed reduced freezing during the early phase of testing, particularly during early inter-trial intervals, although group differences diminished as the session progressed. During subsequent reactivation sessions, control animals maintained robust conditioned freezing, whereas stress-exposed animals exhibited reduced freezing responses to the conditioned cue. Mixed ANOVA revealed a significant effect of day and a stress-by-day interaction that approached significance ($F(1,13)=4.56$, $p=0.052$), suggesting altered expression or stability of conditioned fear memories following retrieval. Behavioral alterations were accompanied by persistent prefrontal cortical transcriptional dysregulation, including changes in glucocorticoid-responsive pathways, activity-dependent plasticity genes, and neuroimmune signaling markers. Together, these findings demonstrate that adolescent chronic stress produces long-lasting effects on fear memory retrieval and reactivation despite intact acquisition, suggesting that stress-related vulnerability may emerge through persistent alterations in prefrontal cortical regulation of memory processes rather than deficits in initial learning.

Disclosures: N. Syme: None. **C. Charpentier:** None. **S. Azerrad:** None. **M. Marcille:** None. **P. Sack:** None. **T. Pantalena:** None. **A.J. Betz:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.15/FF2

Topic: G.03. Stress and the Brain

Support: Binghamton University Faculty Subvention Award

Title: Impact of Adolescent Social Isolation on Pain Sensitivity and Opioid Efficacy

Authors: *D. R. MCCRAY[1], A. N. KARKHANIS[2], G. J. VAUGHAN[3];
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Abstract: Adverse childhood experiences are associated with an increased risk of developing chronic pain and opioid use disorder in adulthood. However, it remains unclear how these adverse experiences during adolescence alter pain processing and responsiveness to opioids as it relates to analgesia and reinforcement. The overarching goal of this study is to investigate the neural pathways that shape pain perception and opioid use. To do so successfully, we need an animal model with face validity. Therefore, here we characterize a clinically relevant rat model of adolescent social isolation, in which male and female Long Evans rats were group-housed (aGH; 4 rats/cage, same sex non-littermates) or isolated (aSI; 1 rat/cage) throughout adolescence (PD 25-69). We then assessed the impact of aSI on oxycodone preference using the conditioned

place preference (CPP) assay. To assess pain sensitivity, following a 3-week washout period, we examined thermal nociception using the Hargreaves assay and measured paw withdrawal latency. Then, after 2 to 3 weeks, we examined mechanical allodynia using von Frey and measured paw withdrawal threshold force before and after an inflammatory injury induced by injecting Complete Freund's Adjuvant (CFA) into the right hind paw. After Day 1 post-CFA assessment, on Day 2, rats were injected with saline or oxycodone (1 mg/kg; i.p.) to assess opioid efficacy in reducing inflammatory pain in aGH and aSI rats. Paw withdrawal thresholds were measured 15 mins after treatment and were assessed for the next 10 days. Male and female aSI rats exhibited greater oxycodone preference compared to aGH rats. Prior to CFA induction, both female and male aSI showed increased thermal nociception, but only female aSI rats exhibited mechanical hypersensitivity. Following CFA injection, all groups exhibited mechanical allodynia, but aSI rats showed an exacerbated response. Furthermore, oxycodone was less efficacious in mitigating mechanical allodynia in aSI compared to aGH rats. All rats showed recovery over the 10-day post-CFA period. In conclusion, aSI was associated with augmented pain sensitivity and a diminished analgesic response to oxycodone, but greater oxycodone preference, which may contribute to poor pain management outcomes and a higher risk of opioid misuse in individuals exposed to adverse experiences during adolescence. These findings highlight the importance of exploring alternative pain treatment approaches that provide effective relief while limiting the potential for opioid misuse, particularly in vulnerable populations.

Disclosures: D.R. McCray: None. **A.N. Karkhanis:** None. **G.J. Vaughan:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.16/FF3

Topic: G.03. Stress and the Brain

Support: Pennsylvania State University salary release funds
National Institutes of Health (Grant T32GM108563)
Biobehavioral Health Department Dissertation Award

Title: Social instability during development exacerbates allergic asthma airway inflammation and glucocorticoid reactivity but ameliorates anxiety-like behavior and central glucocorticoid regulation.

Authors: J. I. CAULFIELD[1], E. COVER[3], J. LIPSCOMB[1], W. J. HORTON[2], H. M. KAMENS[4], *S. A. CAVIGELLI[4];
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Abstract: Allergic asthma is the most common chronic health challenge for youth in the United States, and it occurs during a critical time in neurobiological development when stressors can have long-lasting effects on adult mental health. Prior research has shown separately that youth with asthma and those that experience social instability are at increased risk for developing anxiety. To determine if social instability during development exacerbates asthma-related immune function, anxiety, and/or stress physiology, we used a mouse model to experimentally test the relative influence of allergen-induced airway inflammation and social instability during development on adult asthma and anxiety symptoms. During postnatal days 7-59, BALB/cJ male and female mice were repeatedly exposed to allergen (house dust mite extract) to stimulate airway inflammation, and/or repeated social isolation then novel social partners to simulate social instability, or control conditions. In adulthood, we measured asthma- and inflammation-related circulating cytokines and gene expression in lung tissue, as well as circulating corticosterone at baseline and in response to restraint, anxiety-like behavior, and hypothalamic-pituitary-adrenal (HPA) axis/anxiety-related gene expression in prefrontal cortex and hypothalamus. Social instability exacerbated allergen-induced circulating cytokine concentrations and lung cytokine gene expression and female corticosterone responses to acute stress. However, social instability negated allergen-induced anxiety-like behavior, and prefrontal cortex FKBP5 gene expression in females. Results suggest that repeated social change (or repeated activation of the HPA) during adolescence decreases prefrontal sensitivity to glucocorticoids to produce adults that are resilient to anxiety in the context of allergic asthma.

Disclosures: J.I. Caulfield: None. **E. Cover:** None. **J. Lipscomb:** None. **W.J. Horton:** None. **H.M. Kamens:** None. **S.A. Cavigelli:** None.

Poster

PSTR065: Adolescent Stress: Behavior and Physiology

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR065.17/FF4

Topic: G.03. Stress and the Brain

Title: Assessing power and replicability of behavioral and physiological performance in laboratory mice: A case study on phenotyping strategy for evaluating mouse handling stress

Authors: *J. K. WONG[1], D. R. ADNEY[2], J. M. WOTTON[3], L. L. WATERMAN[2], J. K. WHITE[3];
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Abstract: The principles of 3Rs (replacement, reduction, and refinement) provide guidelines for humane animal research. Alternative mouse handling techniques have been identified as a potential refinement for reducing animal stress. Despite numerous studies on the topic, results across behavioral studies evaluating handling have been variable and have led to questionable replicability. Furthermore, limited studies have investigated the effects of handling in a mouse

production setting. To comprehensively evaluate the impact of handling on mouse welfare, we generated a large breeding colony of C57BL/6J mice handled from birth by one of four handling techniques (tail, hand cupping, tunnel, or scoop and tail) during routine cage changes. Mice were enrolled in either neurobehavioral or cardiophysiology testing to compare the different techniques. Starting at 8 weeks of age, mice (30 male/30 female) underwent a weekly testing pipeline of light/dark, elevated zero maze, spontaneous alternate Y maze, social approach, open field, and tail suspension assays. A second cohort of mice created from breeding pairs of the mice handled by specific techniques from birth also underwent the same neurobehavioral testing to assess generational effects. HD-X11 telemetry devices were subcutaneously implanted in 7-9 male and female mice per group to quantitatively measure heart rate, blood pressure, and temperature at baseline, after a novel handling experience to simulate the customer experience, and after their familiar handling stressor. To evaluate the strength of our sample sizes, power analyses were subsequently performed on assays for a given effect size and to determine variability within the data. Overall, handling technique had no effect on neurobehavioral activity, cognition, depressive-like behavior, anxiety-like behavior, and social behavior, and no effect on mean systolic, diastolic, and mean arterial pressures, heart rate, or temperature at baseline and in response to novel or familiar stressors. We observed batch effects; however, no significant differences were detected when the data were aggregated. To observe a moderate behavioral effect of 20-30% with 80% power, our sample size of 30 mice was sufficient, and no consistent differences were observed. In the second generational cohort, the replicability of the neurobehavioral data was strong and followed similar power trends. Furthermore, to observe a 10% effect for 95% power, the cardiophysiological sample size of 7-8 mice in this study was ideal, demonstrating that we had the power to detect a difference but found none. Altogether, our results showed that handling technique had no effect on animal welfare.

Disclosures: J.K. Wong: None. **D.R. Adney:** None. **J.M. Wotton:** None. **L.L. Waterman:** None. **J.K. White:** None.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.01/FF5

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: R01DA054921

Title: In vitro assessment of blood-brain barrier permeability using Electric Cell-substrate Impedance Sensing (ECIS)

Authors: H. N. WITTORF[1], E. BRAILOIU[2], ***G. C. BRAILOIU**[1];
[1]Thomas Jefferson Univ., Philadelphia, PA; [2]Temple Univ. Sch. of Med., Philadelphia, PA

Abstract: Brain microvascular endothelial cells are an important component of the blood-brain barrier (BBB) and the main regulator of the BBB permeability. *In vitro* assessment of permeability can be performed on endothelial cells grown on porous inserts using tracer flux assays or by measurement of transendothelial electrical resistance (TEER). Electric Cell-substrate Impedance Sensing (ECIS) is a non-invasive technique that allows the automated, real-time measurement and monitoring of impedance, resistance, and capacitance of cells grown on solid substrate, gold electrodes of special arrays. We present the technical details of the ECIS method for assessment of permeability of rat brain microvascular endothelial cells, as an *in vitro* BBB model and examples of changes in monolayer resistance in response to various agonists including SARS-CoV-2 Spike protein. This method provides valuable information about the barrier function that complements morphological studies using immunocytochemistry of tight junctions and *ex vivo* and *in vivo* studies of BBB permeability assessed with Evans Blue and sodium fluorescein, or with miniaturized microscopy (Miniscope), respectively.

Disclosures: H.N. Wittorf: None. **E. Brailoiu:** None. **G.C. Brailoiu:** None.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.02/FF6

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Cross-Modality Validation of an iPSC-Derived Blood-Brain Barrier Model Using Small Molecules, Antibodies, and Antisense Oligonucleotides

Authors: *C. J. M. LOOMANS[1], M. BSIBSI[1], L. VAN BEEK[1], T. YAVUZTURK[2], L. BUTI[1], N. CHUNDURI[1], F. MASMOUDI[1], A.-M. ZUURMOND[1];
[1]IQVIA laboratories, Leiden, Netherlands; [2]IQVIA Labs., Leiden, Netherlands

Abstract: The blood-brain barrier (BBB) serves as a critical protective interface that shields the central nervous system (CNS) from blood-borne toxins and pathogens. However, this same protective function presents a major challenge for CNS drug development, as the BBB severely restricts the entry of most small molecules and biopharmaceuticals into the brain. Consequently, many otherwise promising therapeutics fail to reach effective CNS concentrations, resulting in limited clinical efficacy. There is therefore a strong need for predictive and physiologically relevant in vitro models that can reliably assess brain penetration potential early in drug development. In this study, we evaluated the iCell® Blood-Brain Barrier (BBB) in vitro model, a novel Transwell-based co-culture system comprising human induced pluripotent stem cell (iPSC)-derived brain microvascular endothelial cells, astrocytes, and pericytes. This system is designed to recapitulate key structural and functional features of the human BBB microenvironment. To validate its predictive performance, we assessed the permeability of a panel of small molecules in the iCell model and compared these results to data obtained from a widely used MDR1-overexpressing MDCK cell model, as well as to available in vivo unbound

brain-to-plasma partition coefficients (Kp,uu,brain). In addition, the model's ability to evaluate the brain penetration of larger modalities was investigated by examining the transport of monoclonal antibodies and antisense oligonucleotides (ASOs). Overall, the iCell BBB model demonstrated robust barrier properties and showed promising concordance with in vivo brain penetration data, supporting its utility as a predictive in vitro platform. Although the iCell BBB and MDR1-MDCK models showed differing permeability outcomes with no clear superior system, the iCell BBB model likely provides greater human physiological relevance. These findings highlight the potential of this system for a more comprehensive assessment of CNS drug delivery, spanning both small molecules and biotherapeutics. Future work will focus on applying this model to integrated permeability and toxicity studies, while further benchmarking its performance against in vivo data to assess its translational relevance across multiple therapeutic modalities and strengthen its utility in early-stage CNS drug discovery.

Disclosures: C.J.M. Loomans: None. **M. Bsibsi:** None. **L. van Beek:** None. **T. Yavuzturk:** None. **L. Buti:** None. **N. Chunduri:** None. **F. Masmoudi:** None. **A. Zuurmond:** None.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.03/FF7

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Humanized TFRC and CD98hc mouse models for BBB shuttle to advance antibody and AAV brain delivery

Authors: *Y. SHI;
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Abstract: Receptor-mediated transcytosis (RMT) pathways at the blood-brain barrier (BBB) are widely exploited to enhance central nervous system delivery of biologics and gene therapies. Transferrin receptor (TFRC) remains one of the most extensively investigated BBB shuttle targets; however, its high peripheral expression can contribute to target-mediated drug disposition and undesirable side effects. Consequently, efforts are focused on optimizing TFRC-directed systems and identifying alternative RMT targets. Among these, CD98hc has been associated with prolonged brain retention of therapeutic cargos, while IGF1R and FcRn have also emerged as promising BBB transport targets. To support the translational evaluation of these BBB shuttle strategies, we generated and validated a panel of humanized mouse models expressing the complete human extracellular domains of key BBB transporters, including two TFRC humanized lines generated using distinct genetic engineering strategies, as well as humanized CD98hc models. Humanization of all models was confirmed by qPCR, Western blot, and flow cytometry, demonstrating robust humanized mRNA and protein expression with loss of the corresponding murine extracellular domain. Immunohistochemistry further localized humanized TFRC and CD98hc expression to brain

microvascular endothelial cells, confirming BBB-relevant expression patterns. Functional validation demonstrated efficient antibody transport in both TFRC humanized models. Intravenous administration of an anti-human TFRC bispecific antibody resulted in increased brain cortical accumulation in homozygous humanized mice compared to wild-type controls, confirming active BBB transcytosis. The hTFRC (CDS) model additionally supported BBB delivery of engineered AAV9 vectors targeting human TFRC, as demonstrated by increased mCherry expression and viral genome enrichment in the brain. Similarly, AAV-mediated delivery in the huCD98hc model produced enhanced fluorescence signals in brain tissue relative to controls, indicating functional BBB transport via CD98hc. Together, these results validate both TFRC humanized and huCD98hc models for the evaluation of antibody- and AAV-mediated CNS delivery. Collectively, this panel of humanized models provides a versatile translational platform for preclinical assessment of BBB shuttle technologies and establishes a foundation for future dual-humanized mice to investigate multi-target BBB delivery strategies.

Disclosures: Y. Shi: A. Employment/Salary (full or part-time):; Cyagen Biosciences.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.04/FF8

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Whole-Brain Quantification of BBB-Targeted Biologics Using a Humanized TfR1 (hTFRC) Mouse Model

Authors: A. VICKERS[1], *M. JACOBSON[1], M. ROQUE[2], Y. LIU[2], A. BUTT[2], S. R. STERLACE[1], L. GRIFFIN[1], J. R. RICHARDSON[1], H. H. HANSEN[2], Y. GALLERO-SALAS[2], U. ROOSTALU[2];
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Abstract: Efficient, tissue-specific delivery of biologics remains a major hurdle in therapeutic development. This challenge is especially acute in the central nervous system (CNS), where the blood-brain barrier (BBB) restricts drug access. TfR1-mediated transcytosis has emerged as a strategy to enhance CNS delivery, yet its brain-wide vascular and parenchymal biodistribution is not well quantified at cellular resolution. Moreover, widespread TfR1 expression in peripheral tissues raises concerns about off-target exposure that remain poorly characterized at the whole-organ level. Here, we address these challenges by using a humanized transferrin receptor 1 (hTfR1) mouse model (Taconic Biosciences, strain 23236; hTFRC). Using this model, we combined whole-organ 3D light-sheet fluorescence microscopy (LSFM) with AI-based image analysis to map the biodistribution of four clinically relevant biologics: Trontinemab and Tividenofusp alfa (TfR1-targeted), and Gantenerumab and Efavaleukin alfa (non-TfR-binding controls). Whole brains and hindlimbs were immunolabeled alongside CD31 to visualize vasculature. Deep learning-based segmentation enabled 3D vascular reconstruction and voxel-

level classification of signal in vascular versus parenchymal compartments. Brain-wide antibody quantification was performed using the Allen Mouse Brain Atlas, while hindlimb analysis assessed peripheral exposure in the bone marrow and skeletal muscle, which are TfR1-expressing tissues. Our results indicated modality-dependent differences in antibody distribution. Specifically, TfR1-targeted biologics had enhanced parenchymal brain penetration compared to non-targeted control biologics, which remained largely vascular- or barrier-restricted. Regional analysis revealed heterogeneous distribution across brain and peripheral tissues, highlighting the dual impact of hTfR1 on CNS delivery and systemic exposure in hTFRC mice. This study establishes 1) the hTFRC mouse model as an adequate mouse model system to test biologics and 2) an LSFM and AI-driven platform for unbiased whole-organ biodistribution analysis. Together, this approach allows for simultaneous assessment of BBB transport efficiency, regional brain exposure, and peripheral liabilities to support the design of next-generation BBB-penetrant biologics.

Disclosures: A. Vickers: A. Employment/Salary (full or part-time):; Taconic Biosciences. **M. Jacobson:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **M. Roque:** A. Employment/Salary (full or part-time):; Gubra. **Y. Liu:** A. Employment/Salary (full or part-time):; Gubra. **A. Butt:** A. Employment/Salary (full or part-time):; Gubra. **S.R. Sterlace:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **L. Griffin:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **J.R. Richardson:** A. Employment/Salary (full or part-time):; Taconic Biosciences. **H.H. Hansen:** A. Employment/Salary (full or part-time):; Gubra. **Y. Gallero-Salas:** A. Employment/Salary (full or part-time):; Gubra. **U. Roostalu:** A. Employment/Salary (full or part-time):; Gubra.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.05/FF9

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: High-throughput assessment of BBB function using isogenic human iPSC-derived brain microvascular endothelial cells, astrocytes, and pericytes

Authors: X. XU[1], C. SAVIC[1], M. DONEGAN[1], D. MAJEWSKI[1], R. FIENE[1], J. LIU[1], C. B. CARLSON[1], R. VAIDYANATHAN[1], *E. M. JONES[2,1];
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Abstract: The blood-brain barrier (BBB) is formed by specialized brain microvascular endothelial cells (BMEC) that regulate the transport of substances into and out of the brain. BMEC possess physical, transport, and metabolic properties, which, together with vascular (pericytes), immune, and neural cells, create a tightly controlled central nervous system microenvironment. Understanding BMEC function alone and in combination with other cell types is essential to studying brain health and disease. A key feature of BMEC is their barrier

integrity, often evaluated by measuring electrical resistance across the cell layer. In this study, barrier function of human iPSC-derived BMEC (iCell® Brain Microvascular Endothelial Cells) by itself and in co-culture with iCell Astrocytes 2.0 and iCell Pericytes was assessed using impedance-based and trans-endothelial electrical resistance (TEER) technologies. Cells were differentiated following established protocols from an apparently healthy normal male donor (01279) and cultured on collagen-IV and fibronectin-coated 24- or 96-well inserts. TEER function was evaluated at different seeding densities. Lucifer Yellow permeability assays assessed passive barrier function. To increase throughput, cells were also plated on CytoView-Z plates for continuous impedance-based monitoring using the Maestro Z platform, measuring cell coverage (or confluence) as a resistance at high (41.5 kHz) and a very sensitive TEER at low (1 kHz) frequencies over ten days. TEER values consistently exceeded 1500 Ω·cm² using standard 96-well EVOM™ electrodes, with low Lucifer Yellow permeability observed by day 5. On CytoView-Z plates, real-time impedance monitoring demonstrated ~3500 Ω TEER values at 140 hours, indicating robust barrier integrity and lot-to-lot consistency. This platform enabled profiling of compounds known to disrupt barrier function—including mannitol and VEGF—showing dose-dependent decreases in TEER. These results highlight how human iPSC-derived BMEC only (or in co-culture with pericytes and astrocytes) are a reliable in vitro model for investigating BBB properties and dynamics. Characterizing individual BBB components advances understanding of this complex system's function, facilitating studies in brain physiology and build better in vitro microphysiological systems. The use of high-throughput, sensitive TEER assays with iPSC-derived BMEC provides a robust tool for drug screening and mechanistic studies related to BBB integrity and permeability.

Disclosures: X. Xu: None. **C. Savic:** None. **M. Donegan:** None. **D. Majewski:** None. **R. Fiene:** None. **J. liu:** None. **C.B. Carlson:** None. **R. Vaidyanathan:** None. **E.M. Jones:** None.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.06/FF10

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

Support: NIH Grant 1R01NS136494-01A1
Stony Brook Cancer Center Snyder Fellowship

Title: Chronic Low-Dose Arsenic Exposure Disrupts Vascular Organization and Endothelial Integrity in Human iPSC-Derived Blood Vessel Organoids

Authors: *Y. WANG[1], R. PAN[2], K. J. LIU[2];
[1]Mol. and Cell. Pharmacol., [2]Stony Brook Univ., Stony Brook, NY

Abstract: Arsenic (As) is a widespread environmental contaminant commonly found in drinking water and represents a major public health concern. Chronic As exposure has been associated

with increased risk of vascular diseases, including atherosclerosis, hypertension, peripheral arterial disease, and stroke; however, how chronic As disrupts vascular integrity remains unclear. In this study, human induced pluripotent stem cell (iPSC)-derived vascular organoids served as a physiologically relevant 3D human vascular model. Mature organoids underwent chronic As exposure (0.05, 0.5, and 5 nM) over multiple time points (30-120 days) to assess changes in endothelial organization and vascular integrity. Immunofluorescence analysis revealed marked vascular structural alterations after chronic As exposure. In the absence of arsenic, endothelial cells formed an organized outer layer surrounding a hollow lumen. In contrast, As-treated organoids progressively lost this architecture, resulting in endothelial invasion into the central regionand replacement of the lumen with a dense cell-filled structure. This structural remodeling suggests loss of normal vessel architecture and impaired vessel function. Consistent with these findings, junctional markers showed altered and discontinuous distribution patterns that supported disruption of endothelial organization and vascular integrity. Markers of endothelial identity and polarity similarly lost their organized edge- and lumen-associated localization after As treatment, indicating loss of endothelial organization and lumen-facing polarity. Permeability analysis further showed altered vessel barrier properties after chronic As exposure.
Together, these findings suggest that chronic As exposure progressively disrupts vascular organization, leading to loss of lumen architecture, impaired endothelial integrity, and altered vessel function. These findings provide a potential mechanism for chronic As-induced vascular injury.

Disclosures: Y. Wang: None. **R. Pan:** None. **K.J. Liu:** None.

Poster

PSTR066: Blood Brain Barrier Function and Transport

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR066.07/FF11

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Characterization of an antibody-drug carrier targeted against human ENPEP in a mouse model

Authors: *A. JAFARI[1], R. MUNJI[1], R. DANEMAN[1], M. OLDHAM[2];
[1]Pharmacol., Daneman Lab, Univ. of California San Diego, La Jolla, CA; [2]Neurolog. Surgery, Oldham Lab, Univ. of California San Francisco, San Francisco, CA

Abstract: The blood-brain barrier (BBB) is a tightly regulated interface formed by brain endothelial cells that restricts the passage of substances from the bloodstream into the central nervous system (CNS). It acts as a selective barrier, protecting the brain from xenobiotics including therapeutic drugs and toxins while allowing essential nutrients to enter. To overcome this barrier for drug delivery, our project explores a Trojan horse strategy, which utilizes antibody-membrane protein interactions to transport therapeutic agents across the BBB. Human ENPEP, a membrane protein discovered to be enriched in the endothelial cells of human

glioblastoma, has been identified as a promising target for this approach. In collaboration with Michael Oldham's group, a human anti-human ENPEP (hENPEP) antibody was developed to exploit this target. Daneman Lab created a knockout mouse model for mouse ENPEP. We are optimizing human ENPEP expression through viral delivery. First, we performed viral delivery using retro-orbital injection to express human ENPEP in mouse models. Once human ENPEP expression was established, we administered IgG10, an antibody-drug conjugate specifically designed to bind to hENPEP and deliver the therapeutic payload. This project aims to evaluate the effectiveness of hENPEP as a BBB delivery target and assess the transport properties of the IgG10 antibody in a mouse model. Ongoing work will focus on optimizing antibody expression and assessing therapeutic potential in future experiments.

Disclosures: A. Jafari: None. **R. Munji:** None. **R. Daneman:** None. **M. Oldham:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.01/FF12

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NINDS Grant ZIANS003050-17

Title: Intracranial Venous Drainage, Syrinx Presence, Pain, and Neurologic Function in Chiari I Malformation

Authors: *J. Y. CHOI[1,2], R. MAKWANA[1], C. BRANTLEY[1], M. GUDI[3], J. D. HEISS[1];
[1]Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD; [2]Sch. of Med., Wayne State Univ., Detroit, MI; [3]Detroit Med. Ctr., Troy, MI

Abstract: Introduction: Chiari I malformation is often associated with syringomyelia. Because Chiari I malformation and impaired intracranial venous drainage both affect intracranial compliance, brain volume, and CSF dynamics, we hypothesized that abnormal venous drainage could contribute to syringomyelia in patients with Chiari I malformation.
Methods: Adult patients (median age 34 years; range, 29-42) with Chiari I malformation with (N=11) or without (N=10) syringomyelia were studied. We obtained preoperative cerebral magnetic resonance venography (MRV) and used open-source segmentation software to quantify venous morphology of the superior sagittal sinus, straight sinus, vein of Galen, internal cerebral veins, transverse sinuses, and sigmoid sinuses. Pain scores (Numerical Rating Scale, NRS) and motor and cognitive subtotal scores (Functional Independence Measure, FIM) were obtained in 19 subjects. We compared minimal sinus cross-sectional areas between Chiari I groups with and without syringomyelia using the Mann-Whitney U test. Spearman's correlation was used to evaluate associations between venous diameters and clinical measures.
Results: In patients with syringomyelia, the narrowest part of the superior sagittal sinus was wider (median 13.23 vs. 8.04 mm^2, p=0.026) and less tortuous (median ratio 1.46 vs. 1.57,

p=0.022) than in those without syringomyelia. In contrast, the narrowest part of the right transverse sinus was narrower in patients with syringomyelia (median 18.23 vs. 25.80 mm², p=0.026). Other sinus cross-sectional areas and tortuosity did not differ between groups. Pain (NRS) in Chiari patients with and without syringomyelia ranged from 0 to 8.36; motor subtotal scores ranged from 47 to 91; and cognitive subtotal scores ranged from 16 to 35 (N=19). Vein of Galen maximum diameter correlated with higher cognitive (ρ=0.62, p=0.004) and motor scores (ρ=0.46, p=0.050) and was inversely correlated with pain (ρ= -0.515, p=0.024).
Conclusion: Preoperative MRV-derived venous morphology differed between patients with Chiari I malformation with and without syringomyelia. In patients with syringomyelia, the narrowest superior sagittal sinus area was larger, whereas the narrowest right transverse sinus area was smaller. The Vein of Galen's narrowest diameter was inversely proportional to pain and neurological impairment. These preliminary findings suggest that patients with Chiari I malformation have altered cerebral venous anatomy that may affect syringomyelia development and the severity of neurological symptoms.

Disclosures: J.Y. Choi: A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke. **R. Makwana:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke. **C. Brantley:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke. **M. Gudi:** None. **J.D. Heiss:** A. Employment/Salary (full or part-time):; National Institute of Neurological Disorders and Stroke.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.02/FF13

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: JSPS KAKENHI 25K1856
JSPS KAKENHI 24H02331
JSPS KAKENHI 22H05158
JST-CREST JPMJCR22N4
AMED JP25wm0625422

Title: Structure-Function Coupling Aligns with Multimodal Gradients in the Mouse Cortex

Authors: *R. LI[1], T. MATSUI[1], A. ITO-ISHIDA[2];
[1]Doshisha Univ., Kyotanabe, Japan; [2]RIKEN Ctr. for Brain Sci., Wakoshi, Japan

Abstract: Systematic mismatches between anatomical wiring patterns and brain co-activation patterns provide important clues to elucidate a fundamental principle of cortical organization. In the human brain, the regional heterogeneity of structure-function (S-F) coupling is well characterized by measuring correlations between structural and functional connectivity.

However, the biological mechanisms governing this heterogeneity remain poorly understood. To address this question, we mapped S-F coupling across the mouse cortex by combining structural connectivity derived from axonal tracing data from Allen Mouse Brain Connectivity Atlas (AMBCA) with resting-state functional connectivity measured by wide-field calcium imaging (n = 14). This was then associated with various cortical profiles, including histological features, cellular distributions, and molecular expression patterns. We found that SC and FC were tightly coupled in the mouse cortex (Spearman $r = 0.72$, $R^2 = 0.49$) but also exhibited characteristic regional variations. This variation significantly correlated with multimodal cortical properties, including myelination (T1w/T2w ratio: $r = -0.53$), excitation-inhibition balance (E/I neuron ratio: $r = -0.66$), synaptic density (PSD95 intensity: $r = -0.57$; SAP102 density: $r = -0.51$), and molecular identity (PC1 of 1,055 brain-expressed genes: $r = 0.49$, all $p < 0.05$). In contrast, S-F coupling did not track the anatomically defined cortical hierarchy (feedforward-feedback hierarchical score: $r = 0.16$, $p = 0.44$) or resemble specific cell-type distributions (34 cell classes and 338 subclassed defined in Allen Brain Cell Atlas). As in humans, the S-F coupling in mice was strong in primary sensorimotor areas and weaker in association areas, demonstrating a gradient from unimodal-to-transmodal cortical organization ($r = -0.65$, $R^2 = 0.34$, spatial permutation $p < 0.01$). These findings established graded S-F coupling as a common organizational principle across species, providing a framework for investigating the cellular and molecular drivers of the S-F relationship in mouse models.

Disclosures: R. Li: None. **T. Matsui:** None. **A. Ito-Ishida:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.03/FF14

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CF-2023-I-174

Title: Correlation of fat and iron liver concentrations with brain resting-state networks in prepubertal children

Authors: *B. DE CELIS ALONSO[1], J. MUNDO[2], S. HIDALGO-TOBON[3], P.-W. SO[4]; [1]Fac. of Physical and Mathematical Sci., [2]Fac. of Architecture, Meritorious Autonomous Univ. of Puebla, Puebla, Mexico; [3]UAM-Hospital Infantil de Mexico Federico Gomez, Ciudad DE Mexico, ; [4]Kings Col. London, London, United Kingdom

Abstract: Abstract:
Obesity represents a large public health problem in Mexico and in the whole world (1). The harming effects of obesity and its associated comorbidities, can be grater if they appear sooner in life, like in infancy or preadolescence. Between the large number of comorbidities that appear, non-alcoholic fatty liver disease (NAFLD) as well as iron concentration excess in liver

(hemochromatosis), are two of the most relevant. How they influence brain function and through which physiological mechanisms they do so is still under study. Resting states fMRI imaging (RS-fMRI) is a tool that allows measuring brain function as well as functional connectivity (FC) of a volunteer while staying still in an MR scanner. This research presents a comparative study in which brain RS-fMRI, was performed on a prepubertal population of male children (n=80) with ages between 6 and 10 years. At the same time, liver Iron concentration as well as PDFF (Proton density fat fraction) in liver, were measured with MR imaging commercial protocols. The extent and FC of the Default Mode Network (DMN), Executive Control Network (ECN), Salience, Frontal as well as Thalamic, RS-networks, were correlated to liver fat and iron content as well as BMI. This, trying to establish causality between these parameters and brain function. Preliminary results show that increased PDFF, Iron concentration and BMI was strongly negatively correlated with a decrease of FC between ECN, DMN and Frontal RS-networks ($p<0.05$. parsons' correlation tests in all cases). This theoretically suggests that fat and iron levels modulate brain function maybe though neuroinflammation.

Disclosures: B. De Celis Alonso: None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.04/FF15

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Restrain stress enhances LC-PVH functional connectivity

Authors: *A. J. PARK;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Stress constitutes a fundamental physiological state that supports homeostatic integrity and adaptive behavioral responses to environmental demands. The locus coeruleus (LC), the primary source of norepinephrine (NE) in the brain, is a key regulator of stress-related neural activity and projects widely throughout the brain, including the central amygdala (CeA), medial prefrontal cortex (mPFC) and lateral septal nucleus (LS). However, while stress-induced alterations in individual brain regions have been extensively investigated, whole-brain connectivity dynamics and their persistence following stress remain insufficiently understood. Here, we employed functional ultrasound imaging (fUS) to monitor whole-brain hemodynamic changes before, during, and following restraint stress in mice. We observed a progressive increase in functional connectivity between the LC and PVH from the pre-stress to post-stress period, whereas LC connectivity with the CeA, mPFC, and LS remained unchanged. These findings suggest that acute stress induces persistent alterations in LC-PVH network dynamics, highlighting a potential circuit mechanism underlying sustained stress responses.

Disclosures: A.J. Park: None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.05/Web Only

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Propofol anesthesia is associated with altered resting-state network dynamics across spectral, spatial, and temporal domains linked to states of consciousness

Authors: *B. JARRAHI;
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Abstract: Anesthesia provides a powerful experimental framework for probing the neurobiology of consciousness. Previous fMRI work has demonstrated that anesthesia disrupts connectivity between association cortices, but conventional paradigms remain constrained in their ability to detect spatiotemporal changes in brain network architecture across different states of consciousness. In this study, we leveraged an openly available fMRI dataset (OpenNeuro accession: ds006623) from 25 healthy participants (12 females; mean age 25.24 ± 4.01 years) undergoing graded propofol sedation. We focused on resting-state acquisitions before (Rest 1) and after (Rest 2) propofol administration, applying high-dimensional independent component analysis (ICA; 75 components), combined with multivariate analysis of covariance (MANCOVA) to identify resting-state networks (RSNs) and characterize anesthesia-related changes. We examined RSNs across three canonical outcome measures at a Bonferroni-corrected $p < 0.05$: spatial map intensity, time-course spectral power, and static functional network connectivity (sFNC). Dynamic FNC (dFNC) was also assessed using a sliding-window correlation approach and k-means clustering. Following propofol anesthesia (Rest 2 vs. Rest 1), spatial analyses revealed enhanced within-network connectivity in the sensorimotor (SMN) and subcortical networks (SCN; amygdalohippocampal regions). Spectral analyses showed increased low- to mid-frequency power in SMN, SCN, and cognitive-attention networks (including central executive, dorsal and ventral attention, salience, self-referential, and posterior default mode networks), as well as decreased mid- to high-frequency power in the basal ganglia, anterior default mode, and frontal networks. Static connectivity analyses revealed decreased sFNC between SMN components, and reduced connectivity between the orbitofrontal cortex and middle temporal gyrus (MTG), and between MTG and the anterior default mode network. In contrast, increased connectivity was observed between the central executive network (CEN) and SMN, and between the salience network and SCN (thalamus). Dynamic connectivity analyses further revealed state-dependent alterations, including increased dFNC between SMN and CEN, decreased coupling between SCN and salience network, reduced frontal-salience interactions, and disrupted connectivity involving orbitofrontal, temporal, and default mode regions. These preliminary results offer novel perspectives on how anesthesia can modify resting-state brain network dynamics with quantifiable alterations across spectral, spatial and temporal domains.

Disclosures: B. Jarrahi: None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.06/FF16

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Tracing early childhood environment in resting-state functional networks

Authors: *E. HAYDAY[1], M. GELL[1], J. LEHMAN[1], J. MOSER[2], K. IP[3], S. MAREK[4], D. A. FAIR[2], B. TERVO-CLEMMENS[1];
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Abstract: It has been well-established that the early childhood environment impacts later physical and mental health. Environmental measures such as childhood stress, family dynamics, and neighborhood context can be traced in functional networks in older adolescents; however, it is unclear when these patterns first emerge. In this study, we examine the relationship between neighborhood environment, perinatal health, and functional networks in infancy. We utilized data from the first postnatal visit (0-1 month old) of the Healthy Brain and Child Development (HBCD) study. Area deprivation index (ADI), a measure of neighborhood socioeconomic disadvantage, was acquired through geocoded address data, and birthweight, a predictor of infant health, was acquired in a survey collected at the first postnatal visit. Connectivity data were generated from minimally preprocessed resting-state fMRI data using fMRIPrep and XCPD pipelines. After motion scrubbing, a minimum of 8 minutes of low-motion (<0.2mm FD) data was used for each participant. Finally, vertexwise time series were parcellated using the Gordon atlas, and functional connectivity between regions was calculated using Pearson correlation and fisher z-transformed. Ridge regression was used to fit whole-brain prediction models. Model training was performed using a 5x5 nested cross-validation scheme. Feature-wise confound removal of sex and age was performed using linear regression within each training fold, and the confound models were applied to held-out test data to prevent data leakage. Regression weights were Haufe-transformed, and out-of-sample model performance was assessed for significance against a permutation-based null distribution (1000 repeats). ADI (N=487) and birthweight (N=642) were both predicted out-of-sample with moderate accuracy (ADI r=0.405; birthweight r=0.245). Predictions were statistically significant for birthweight (p=0.001) and trended towards significance for ADI (p=0.083). Haufe-transformed feature weights for both ADI and infant birthweight were highest in sensorimotor regions, where ADI showed a negative correlation, and birthweight showed a positive correlation with FC. ADI and birthweight were not significantly correlated in this sample (r=-0.056, p=0.22). These neural patterns support findings in adolescents, suggesting that environmental context is correlated with neural activity already in early childhood and that these relationships may show continuity across the lifespan. A better understanding of how the environment shapes functional network development may provide valuable insight into the pathophysiology of psychiatric disorders.

Disclosures: E. Hayday: None. **M. Gell:** None. **J. Lehman:** None. **J. Moser:** None. **K. Ip:** None. **S. Marek:** None. **D.A. Fair:** None. **B. Tervo-Clemmens:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.07/FF17

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

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

Title: Long-term dynamics of BOLD-perfusion coupling in Parkinson's disease treated with subthalamic nucleus deep brain stimulation

Authors: *Y. WU[1], Y. FAN[1], J. PENG[1], H. TIAN[3,1,4], G. ZHANG[1], Y. LIU[1,4], L. GUAN[1], H. YU[1], L. LI[1,2];
[1]Natl. Engin. Res. Ctr. of Neuromodulation, [2]IDG/McGovern Inst. for Brain Res., Tsinghua Univ., Beijing, China; [3]Col. of Future Technol., Peking Univ., Beijing, China; [4]Changping Lab., Beijing, China

Abstract: Subthalamic nucleus deep brain stimulation (STN-DBS) induces profound circuit-level functional remodeling in Parkinson's disease (PD). While resting-state blood oxygenation level-dependent (BOLD) MRI routinely captures these network dynamics, it remains unclear whether these signals reflect true underlying tissue perfusion (cerebral blood flow, CBF) or represent independent neuroplastic processes during long-term postoperative adaptation. We hypothesized that post-DBS longitudinal remodeling exhibits a functional-perfusion dissociation, where BOLD dynamics and CBF reflect distinct components of network adaptation across different therapeutic states. We acquired paired longitudinal resting-state BOLD and arterial spin labeling (ASL) MRI from 7 participants with PD after bilateral STN-DBS, across five postoperative visits spanning 1 year under Med-Off/DBS-Off, Med-Off/DBS-On, and Med-On/DBS-On states. Local BOLD dynamics were quantified using amplitude of low-frequency fluctuations (ALFF), fractional ALFF (fALFF), and regional homogeneity (ReHo); CBF was extracted from matched regions. Analyses used linear mixed-effects models with FDR correction. Longitudinal models revealed that post-DBS remodeling is highly sensitive to the immediate treatment context, showing striking BOLD changes but limited concurrent CBF shifts. In the Med-Off/DBS-On state, longitudinal effects were widespread, involving progressive decreases in ALFF/fALFF over time ($q<0.05$), indicating a long-term stabilization or adaptation to chronic stimulation. Conversely, combined therapy (Med-On/DBS-On) exhibited remarkable functional stability across 12 months. Crucially, longitudinal BOLD trajectories were largely discordant with CBF profiles. Instead, regional neurovascular coupling was highly selective: localized ReHo-CBF coupling was captured specifically during DBS activation within deep-circuit nodes (GPi: $r=0.38$,$p=0.007$; GPe: $r=0.36$,$p=0.010$) and the cerebellum ($r=0.30$,$p=0.018$). These findings demonstrate that postoperative brain remodeling after STN-

DBS involves distinct amplitude- and synchrony-related functional adaptations. The marked dissociation between overall BOLD trajectories and CBF, paired with focal ReHo-CBF coupling in basal ganglia-cerebellar loops, suggests that local neural synchrony (ReHo)—rather than BOLD fluctuation amplitude—is the primary driver of perfusion-linked energetic demands during DBS. This provides critical insights into the neurovascular mechanisms underlying therapeutic neuromodulation.

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

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.08/FF18

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Private philanthropy: Sammons Enterprises, Inc. and the Hoglund Foundation

Title: Neurovascular response features predict 6-month changes in BrainHealth Index and component factors

Authors: *A. EBRAHIMI[1,2], D. BHATIA[2], J. SPENCE[1];
[1]Ctr. for BrainHealth, Sch. of Behavioral and Brain Sci., [2]Dept. of Electrical and Computer Engin., Univ. of Texas at Dallas, Dallas, TX

Abstract: The BrainHealth Index (BHI) is a multidimensional measure of brain health that includes social connectedness, emotional well-being, and cognition. Although these reflect factor analytic domains from non-imaging tests and questionnaires, it remains unclear whether 6-month changes in the BHI are reflected in objective neurovascular signals. We tested whether imaging-derived biomarkers from breath-hold and visual checkerboard fMRI tasks, cerebral blood flow (CBF), and structural MRI could predict changes in overall BHI and its component factors. The sample included 60 adults, 28 men and 32 women, ages 21 to 70. For the prediction analysis, we used de-identified longitudinal data from participants with available BHI scores and neuroimaging features at T1 and T2. Breath-hold and checkerboard task data were used to extract voxel-wise hemodynamic response features, including peak amplitude, area under the curve, full width at half maximum, undershoot depth and latency, and pre-peak dip measures. These features were summarized across activated voxels using mean, median, standard deviation, minimum, and maximum values. Additional predictors included gray and white matter CBF, basal CBF metrics, and structural MRI measures from hippocampus, amygdala, insula, cortical thickness, and total gray and white matter volumes. Gradient boosting machine and stacked ensemble models were trained with five-fold cross-validation and evaluated using repeated 80/20 train-test splits. Prediction of 6-month change was strongest for the cognitive factor (F3) and overall BHI. Across repeated splits, the F3 model achieved a mean test R^2 of 0.33 ± 0.15, while

the overall BHI model achieved $R^2 = 0.22 \pm 0.14$. The social connectedness factor (F1) also showed predictive signal, with $R^2 = 0.29 \pm 0.15$, whereas the emotional well-being factor (F2) showed weaker and less stable prediction, with $R^2 = -0.17 \pm 0.34$. The best individual splits reached $R^2 = 0.61$ for F3, 0.50 for F1, 0.41 for overall BHI, and 0.14 for F2. Important predictors included breath-hold and checkerboard peak amplitude variability, median amplitude, AUC variability, undershoot depth variability, and latency-related features, along with contributions from insula and white matter volume. Together, these findings suggest that task-based neurovascular response features may help predict short-term changes in brain health, particularly for the cognitive factor and the overall BHI. However, performance varied across train-test splits, indicating that larger samples and participant-level validation are needed before these biomarkers can be used to reliably estimate individual BHI trajectories.

Disclosures: A. Ebrahimi: None. **D. Bhatia:** None. **J. Spence:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.09/FF19

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: RF1NS124778
R01NS122904

Title: A Vascular-Free Living Organoid Platform for Validating Neural Activity-Related Sodium (NARS) fMRI Signals at 15.2 T

Authors: E. ARSENAULT, G. YU, ***X. LIU**, D. HIKE, N. PASUPATHY, X. A. ZHOU, X. YU;
Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Neuronal activity-related sodium functional MRI seeks to detect sodium signals linked to neuronal activity beyond hemodynamic readouts, but in vivo validation is limited by vascular and systemic confounds. We developed a vascular-free living human cortical organoid platform for validating neural activity-related sodium-23 MRI signals at the 15.2 T scanner. Prior work established high-field 1H/23Na MRI of fixed organoids, demonstrating co-registered structural/diffusion imaging and 23Na biexponential relaxation maps sensitive to heterogeneous ionic microenvironments (Fig. 1). Building on this foundation, we engineered an MRI-compatible perfusion bioreactor that maintains living organoids in physiological media with thermal regulation and optical access for stimulation/readout during MRI (Fig. 2). This platform enables controlled manipulation of neural activity while measuring MRI signal changes in living tissue lacking vasculature, allowing ionic/neural contributions to be separated from hemodynamic effects. Ongoing studies will test whether organoid sodium dynamics track neuronal activation and benchmark NARS-fMRI mechanisms under controlled conditions. This

system bridges cellular neurophysiology, multinuclear MRI, and mechanistic validation of neural activity-related functional imaging.

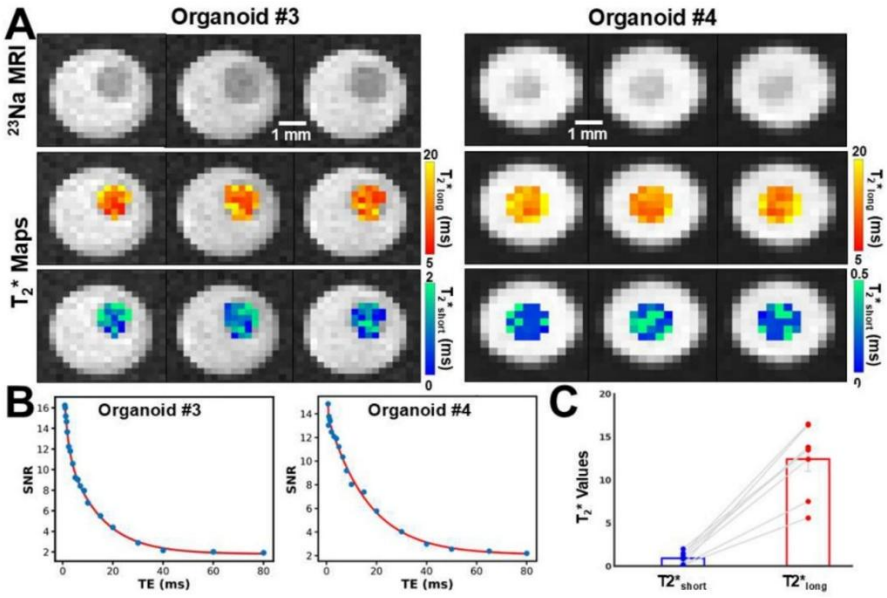


Figure 1. Fixed-organoid 23Na MRI foundation

Prior fixed-organoid high-field multinuclear MRI demonstrated sodium-weighted imaging and biexponential 23Na relaxation mapping, revealing heterogeneous ionic microenvironments in vascular-free cortical organoids.

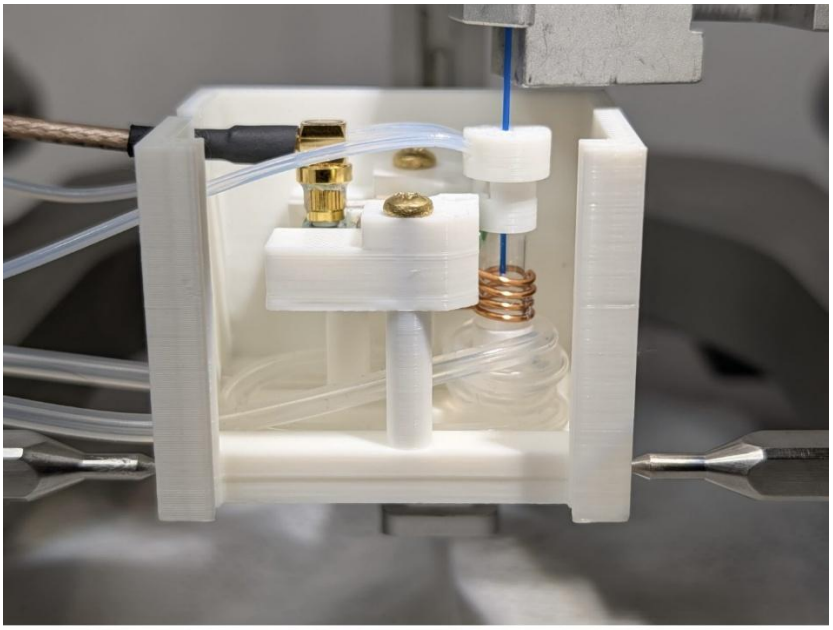


Figure 2. MRI-compatible living organoid bioreactor

The bioreactor supports living organoid MRI through media perfusion, thermal regulation, RF coil stabilization, and optical access for stimulation or readout during imaging.

Disclosures: E. Arsenault: None. **G. Yu:** None. **X. Liu:** None. **D. Hike:** None. **N. Pasupathy:** None. **X.A. Zhou:** None. **X. Yu:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.10/FF20

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant R21HD109722

Title: Food for Thought: Habitual Dietary Patterns and Gray Matter Volume in Adults

Authors: *S. V. ROCHE[1], M. BAUGH[2], M. AHRENS[3], A. G. DIFELICEANTONIO[2]; [1]Virginia Tech. Carilion Sch. of Med., Roanoke, VA; [2]Virginia Tech., Roanoke, VA; [3]Univ. of Kansas Med. Ctr., Olathe, KS

Abstract: Title: Food for Thought: Habitual Dietary Patterns and Gray Matter Volume in Adults
Authors: Sophia Roche, Emma Leslie, Maria Rego, Zachary Hutelin, Mary Elizabeth Baugh, Monica Ahrens, Brenda Davy, Alexandra DiFeliceantonio
Recent studies demonstrate a negative association between ultra-processed food (UPF) diets and gray matter volume (GMV), suggesting possible neurodegenerative effects. However, less is known regarding acute and longer-term effects of habitual diet on GMV. The objective of this study is to evaluate the relationship between UPF diet and GMV, as it remains unclear whether UPF consumption exerts acute, causal effects on brain structure independent of confounding lifestyle and nutritional factors.
Participants completed two 14-day controlled feeding periods (81% UPF vs. 0% UPF) with a 4-week washout period. The two diets were matched for macronutrients, diet quality, and energy density. T1-weighted MRI scans were acquired pre- and post-intervention and processed using CAT12 voxel-based morphometry. A 2x2 within-subject ANOVA (diet x time) was performed with total intracranial volume (TIV) and age as covariates. Region-of-interest (ROI) analyses included the amygdala, cingulate gyrus, frontal lobe, hippocampus, hypothalamus, insula, striatum, and thalamus.
Twenty-two individuals aged 18-25 years (mean BMI = 23.7 kg/m^2) were included. Mean daily calories from UPF were 897.2 (range: 382.1-1856.0) and mean percent of dietary UPF was 57.7% (range: 28.1%-83.5%). No significant effect of diet, time, or diet x time interactions in GMV were observed within predefined ROIs. Whole-brain exploratory analyses similarly revealed no significant effects.
Short-term consumption of a UPF-rich diet, compared to a minimally processed diet, did not produce detectable macrostructural changes in GMV in a healthy young adult sample. These findings suggest that previously reported associations between UPF intake and reduced GMV may reflect longer-term exposure or cumulative effects rather than acute structural alterations. Subtle or microstructural changes not captured by VBM cannot be excluded.

Disclosures: S.V. Roche: None. **M. Baugh:** None. **M. Ahrens:** None. **A.G. DiFeliceantonio:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

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Program #/Poster #: PSTR067.11/FF21

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH/NIA R37AG033906
NIH/NIA R01AG081479
NIH/NIA R01AG067757

Title: Mechanism-based clinical pain phenotypes differ in functional brain connectivity and psychosocial profiles in symptomatic knee osteoarthritis

Authors: *E. L. TERRY[1], B. C. EZE[2], B. R. GOODIN[5], Y. CRUZ-ALMEIDA[3], R. B. FILLINGIM[2], J. J. TANNER[4];
[2]Pain Res. and Intervention Ctr. of Excellence (PRICE), [3]Inst. on Aging, [4]Clin. and Hlth. Psychology, [1]Univ. of Florida, Gainesville, FL; [5]Dept. of Anesthesiol., Washington Univ., Saint Louis, MO

Abstract: Symptomatic knee osteoarthritis is associated with chronic pain and contributes to multiple years lived with disability. Chronic knee pain varies between patients due to the influence of multiple psychosocial risk (pain catastrophizing, depression) and resilience (optimism) factors. In this longitudinal study, we used mechanism-based clinical phenotypes to classify patients with knee pain into predominant nociceptive, neuropathic, or nociplastic pain groups, or mixed neuropathic/nociplastic pain groups, and to investigate their respective clinical and psychosocial profiles at baseline and 2 years later. Community-dwelling adults with knee osteoarthritis (n=177) completed questionnaires, function performance, and neuroimaging. Cluster analysis was used to identify pain profiles, and analysis of covariance was conducted to assess differences across pain groups in clinical pain and disability, and psychosocial risk and resilience outcome variables. Additionally, resting-state fMRI analyses were conducted to characterize whole-brain intrinsic connectivity differences between the pain groups. Results revealed significant group differences in psychosocial risk [catastrophizing ($F = 12.2$, $p < 0.001$), depression ($F = 9.74$, $p < 0.001$)] and resilience [optimism ($F = 1.97$, $p = 0.120$)] factors, clinical pain [($F = 18.91$, $p < 0.001$)], disability [($F = 16.62$, $p < 0.001$)], and functional performance [($F = 2.24$, $p = 0.086$)], controlling for sociodemographic covariates. Indeed, the mixed neuropathic/nociplastic pain group showed the poorest outcomes. Two years later, there were group differences in multiple measures, including psychosocial risk [catastrophizing ($F = 12.66$, $p < 0.001$), depression ($F = 2.76$, $p = 0.045$)], clinical pain [($F = 6.46$, $p < 0.001$)] and disability [($F = 6.28$, $p < 0.001$)], and movement-evoked pain [($F = 7.93$, $p < 0.001$)]. The neuropathic group showed reduced brain connectivity in regions associated with the dorsal attention and

visual networks, compared with the nociceptive group. In contrast, we observed differences in the default mode and frontoparietal networks between the neuropathic/nociplastic and nociceptive groups. Together, these findings demonstrate that mechanism-based pain profiles may be associated with distinctive clinical and psychosocial risk and resilience factors that may differentiate these pain groups. These clinical, behavioral, and neurobiological profiles may have clinical utility and can be used to optimize a biopsychosocial framework for assessment, diagnosis, and treatment of individuals with symptomatic knee osteoarthritis. Future research should investigate the mixed pain groups.

Disclosures: E.L. Terry: None. **B.C. Eze:** None. **B.R. Goodin:** None. **Y. Cruz-Almeida:** None. **R.B. Fillingim:** None. **J.J. Tanner:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.12/FF22

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: MOST-114-2410-H-028-007-

Title: Effects of Acute Exercise on Brain Glutamate, GABA, and Lactate Concentrations: A Systematic Review and Meta-Analysis of Magnetic Resonance Spectroscopy Studies

Authors: *Y.-C. CHEN[1], Y. CHEN[2,3];
[1]Physical Educ., [2]Natl. Taiwan Univ. of Sport, Taichung, Taiwan; [3]Nuclear Med. Imaging Section, China Med. Univ. Hosp., Taichung, Taiwan

Abstract: Acute aerobic exercise has been shown to improve cognitive function, mood, and psychological well-being; however, the underlying neurochemical mechanisms remain incompletely understood. Proton magnetic resonance spectroscopy (1H-MRS) provides a non-invasive approach for quantifying exercise-induced changes in brain metabolites and neurotransmitters. The present study systematically reviewed and synthesized evidence regarding the effects of acute exercise on cerebral glutamate (Glu), glutamate-glutamine complex (Glx), gamma-aminobutyric acid (GABA), and lactate (Lac) concentrations.A systematic literature search was conducted in PubMed and Scopus through May 2026 following PRISMA guidelines. Search terms combined acute exercise, magnetic resonance spectroscopy, glutamate, GABA, Glx, and brain metabolites. Eligible studies included human participants undergoing a structured acute exercise intervention with neurochemical outcomes assessed using 1H-MRS. Data regarding participant characteristics, exercise protocols, brain regions, and neurochemical outcomes were extracted and qualitatively synthesized.Seven studies met inclusion criteria. Across studies, acute aerobic exercise consistently increased cerebral lactate concentrations. Significant elevations in Glu and/or Glx were observed in the occipital cortex, primary visual cortex, anterior cingulate cortex, parietal cortex, and prefrontal cortex. Specifically, previous

studies reported increases ranging from 11-18% in Glu/Glx concentrations following exercise. In contrast, one study reported no significant changes in occipital Glu or glutamine concentrations. Acute exercise also increased GABA concentrations in the primary visual cortex and sensorimotor cortex, with one study demonstrating a 20% increase in sensorimotor GABA. Furthermore, a single yoga session was associated with elevated whole-brain GABA levels. Overall, findings suggest region-specific modulation of excitatory and inhibitory neurotransmission following acute exercise.These findings indicate that acute exercise induces robust neurochemical responses characterized by increased glutamatergic activity, enhanced GABAergic signaling, and elevated cerebral lactate metabolism. Exercise-related alterations in excitatory-inhibitory balance and brain energy metabolism may represent important mechanisms underlying the beneficial effects of physical activity on brain function and mental health. Future studies employing larger samples and standardized MRS methodologies are warranted to further elucidate the neurobiological mechanisms of exercise.

Disclosures: Y. Chen: None. **Y. Chen:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.13/FF23

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Behavioral and MRI neuroimaging effects of short-term intermittent hypoxia and psilocybin treatment in awake mice

Authors: *R. AHUJA[1,2], A. KOGANOV[3], E. BENNET[3], T. NELSON[3], K. BALAJI[4], L. WILLIAMSON[3], M. A. GITCHO[6], S. HATFIELD[3], P. P. KULKARNI[5], C. F. FERRIS[5]; [1]Ctr. for Translational NeuroImaging, Boston, MA; [2]Behavioral Neurosci., [3]Northeastern Univ., Boston, MA; [4]Northeastern Univ., San Jose, CA; [5]Psychology, Northeastern Univ., Boston, MA; [6]Biol. Sci., Delaware State Univ., Ocean City, MD

Abstract: The effects of intermittent hypoxia (IH), or alternating periods of normoxia and hypoxia, often depend on the dose, severity, and duration of IH cycles. While chronic sleep-apnea-related IH can increase oxidative stress, inflammation, and apoptosis, brief IH can offer protection against hypoxic cognitive dysfunction through neuroplastic and neurovascular remodeling. Psilocybin, a psychedelic natural tryptamine alkaloid found in mushrooms, is similarly associated with enhanced synaptic plasticity through 5-HT2A receptor agonism and downstream pathways involved in cortical plasticity and restructuring.To evaluate how psilocybin administration modifies the similarly related behavioral and neuroconnectivity effects of short-term IH, we exposed four cohorts of male and female mice to seven days of IH (9-21% O_2 cycling every 14 minutes, 6 hours/day) or normoxia (21% O_2, 6 hours/day) and subsequently administered psilocybin (3 mg/kg, IP) or vehicle controls. We then conducted the open field test, novel object recognition, and y-maze behavioral tests followed by anesthetized diffusion

weighted imaging (DWI) and fully awake functional connectivity (FC) MRI imaging. To preserve wake-state translational outcome measures, IH/normoxia exposure occurred during the light cycle and behavioral testing and awake functional MRI were performed during the dark cycle.Interestingly, behavioral findings indicate that moderate IH increased hyperactivity and object memory, and psilocybin maintained the IH-associated increase in object memory and exploratory activity but did not reverse anxiety-like behavior. DWI revealed significantly elevated apparent diffusion coefficients following IH, while volumetric analyses suggested selective regional changes in the IH + psilocybin group. FC analyses suggested psilocybin-sensitive changes in network organization, while tissue-level characterization of vascular integrity and neuroinflammatory markers will further clarify the biological mechanisms underlying these effects.

Disclosures: R. Ahuja: None. **A. Koganov:** None. **E. Bennet:** None. **T. Nelson:** None. **K. Balaji:** None. **L. Williamson:** None. **M.A. Gitcho:** None. **S. Hatfield:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PPK has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.14/FF24

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Awake Animal MRI: The Drug-Naïve Brain on Psychedelics

Authors: *N. J. CAVALLARO[1], R. J. ORTIZ[3], S. SOLTANPOUR[4], P. P. KULKARNI[2], C. F. FERRIS[2];
[2]Psychology, [1]Northeastern Univ., Boston, MA; [3]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL; [4]Carleton Univ., Ottowa, ON, Canada

Abstract: Human psychedelic neuroimaging is inherently confounded by prior drug exposure, expectation, and subjective experience, obscuring the primary pharmacological actions of these compounds. Awake, drug-naïve rodent pharmacological MRI (phMRI) offers a controlled translational model that eliminates anesthetic interference, circadian mismatch, and expectation bias, providing a physiological state that more closely parallels the human awake condition. Here we present a compound-level characterization of brain-wide BOLD responses and resting-state functional connectivity (rsFC) across six serotonergic psychedelics and related psychoactive compounds (LSD, psilocybin, mescaline, DMT, 5-MeO-DMT, and ibogaine) administered

intraperitoneally to fully conscious male and female Sprague-Dawley rats during the active phase of their circadian cycle. All data were registered to a 3D rat brain atlas with ~170 segmented regions, enabling site-specific quantification of global activity and large-scale network reorganization. Despite shared serotonergic agonist properties, each compound produced a distinct neurobiological signature. Acute BOLD responses diverged in both direction and spatial distribution across compounds, ranging from dose-dependent negative BOLD with delayed corticothalamic and cerebellar hyperconnectivity, to robust positive BOLD activation with global hyperconnectivity and sex-dependent sensitivity. Differential engagement of cortical, thalamic, hippocampal, and cerebellar circuits was observed in a compound-specific manner, with the cerebellum emerging as a consistently engaged but underappreciated node. Rather than supporting a unified psychedelic mechanism, these findings reveal the neurobiological individuality of each compound. This work establishes a controlled translational baseline for dissociating the primary pharmacological actions of individual psychedelics from experiential and contextual confounds, with direct relevance to mechanism-based therapeutic development.

Disclosures: N.J. Cavallaro: None. **R.J. Ortiz:** None. **S. Soltanpour:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging..

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.15/FF25

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Ibogaine Induced Dose-Dependent Changes in Global Brain Activity and Connectivity Using fMRI

Authors: *R. RIENECKER[1], N. CAVALLARO[1], N. RAO[1], A. STEFANSKI[1], H. MUKHTAR GHUMMAN[1], R. J. ORTIZ[3], S. SOLTANPOUR[4], D. MADULARU[5], P. P. KULKARNI[2], C. F. FERRIS[2];
[1]Pharmaceut. Sci., [2]Psychology, Northeastern Univ., Boston, MA; [3]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL; [4]Carlton Univ., Ottawa, ON, Canada; [5]McGill, Ottawa, ON, Canada

Abstract: Ibogaine is a naturally occurring psychoactive indole alkaloid with proven anti-addictive effects in treating Substance Use Disorder (SUD). However, the dose-dependent effects of Ibogaine on whole-brain neural activity and functional network connectivity has never

been directly characterized using neuroimaging. Via IP injection, Ibogaine was administered to drug naive Sprague-Dawley rats as Vehicle, 1.0, 5.0, and 25 mg/kg Ibogaine HCl. A fully awake Pharmacological MRI and resting-state functional connectivity (rsFC) analysis was performed, and changes in BOLD signal volume of activation was quantified across 169 atlas-defined brain areas. Ibogaine produced a biphasic dose-dependent effect on whole-brain positive BOLD volume of activation, with suppression at 5 mg/kg and widespread activation at 25 mg/kg relative to vehicle. At 25 mg/kg, significant increases in positive BOLD volume of activation were observed in thalamic nuclei, retrosplenial and somatosensory cortices, cerebellum, and brainstem, while the ventral tegmental area and substantia nigra compacta showed near-complete suppression. Resting-state analysis revealed dose-dependent global hyperconnectivity at 25 mg/kg, with dopaminergic nuclei creating new functional connections across cortical, limbic, and cerebellar regions, but not the basal ganglia. Ibogaine engages the neural circuits of addiction at their source, suppressing dopaminergic reward circuitry while producing global network hyperconnectivity and activating thalamic and cerebellar sensory filtering circuits. These findings provide the first neuroimaging characterization of ibogaine's dose-dependent brain effects and establish testable biomarkers for future behavioral and clinical trials, explanations why Ibogaine may have anti-addictive properties, and the clinical potential for mitigating withdrawal symptoms associated with SUD.

Disclosures: R. Rienecker: None. **N. Cavallaro:** None. **N. Rao:** None. **A. Stefanski:** None. **H. Mukhtar Ghumman:** None. **R.J. Ortiz:** None. **S. Soltanpour:** None. **D. Madularu:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PPK has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging..

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.16/FF26

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Dose-dependent changes in global brain activity and functional connectivity following exposure to DMT: a BOLD MRI study in awake rats.

Authors: *S. D'ARGENIO[1], N. CAVALLARO[1], R. J. ORTIZ[3], S. SOLTANPOUR[4], P. P. KULKARNI[2], C. F. FERRIS[2];
[2]Psychology, [1]Northeastern Univ., Boston, MA; [3]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL; [4]Carleton Univ., Ottowa, ON, Canada

Abstract: N,N-dimethyltryptamine (DMT) is a naturally occurring tryptamine found in various plants and mammalian tissues that acts as an agonist at multiple serotonin (5-HT) receptor subtypes, including 5-HT1A, 5-HT2A, and 5-HT2C, as well as at sigma-1 receptors and trace amine-associated receptor 1 (TAAR1). Its potent psychedelic effects are primarily attributed to agonism at the 5-HT2A receptor, at which DMT displays particularly strong affinity and efficacy relative to its other targets. When administered parenterally, DMT produces a rapid and intense but short-lived psychedelic state characterized by vivid visual imagery, altered sense of self, and ego dissolution in humans. Recreationally, DMT is usually smoked or vaporized for its brief but intense effects, and it is increasingly consumed orally as a component of ayahuasca, a plant-based brew with deep roots in Amazonian ceremonial traditions that has seen a substantial increase in global use in recent decades. Growing evidence suggests DMT may also engage circuits underlying reward and motivation, though the brain circuitry of these effects remains poorly characterized. To examine the effects of DMT on global brain activity and resting state functional connectivity with particular attention to reward and motivation circuitry, we conducted a pharmacological MRI (phMRI) study in fully awake male and female rats. Forty-eight rats (24 male, 24 female) were assigned to one of four groups and received a single IP injection of vehicle, 1, 2.5, or 7.5 mg/kg DMT during scanning. We observed dose-dependent modulation of BOLD signal and functional connectivity in regions associated with reward and motivation. These findings help characterize the neurobiological mechanisms underlying DMT's therapeutic potential in disorders marked by reward and motivational dysregulation, complementing ongoing clinical trials investigating extended-state DMT as a novel treatment for depression and anxiety.

Disclosures: S. D'Argenio: None. **N. Cavallaro:** None. **R.J. Ortiz:** None. **S. Soltanpour:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PPK has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF has a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases and analytical software for use in awake animal imaging..

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.17/FF27

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: DoD CDMRP W81XWH-16-2-0054

Title: High performance head gradients with high gradient strength and SR=500 slew rate enhance network detection, signal sensitivity, and resolution in multi-echo resting state functional magnetic resonance imaging

Authors: J. SHAO, K. SODERLUND, C. VOJTA, T. YUAN, *H. D. MORRIS;
Radiology and Bioengineering, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Motivation/problem statement: Multi-echo (ME) resting-state fMRI (rs-fMRI) improves signal differentiation from physiological noise over single-echo (SE) acquisitions but is traditionally limited by trade-offs between repetition time (TR), spatial resolution, and temporal Signal-to-Noise Ratio (tSNR). High-performance head gradient (HPHG) MRI systems address this via faster slew rates. This study demonstrates how HPHG scanners enhance ME rs-fMRI speed, sensitivity, resolution, and network detection. **Methods/ approach:** Twenty participants (mean age: 38.3 +/- 10.7 years; 13 females) were scanned on a GE MAGNUS 3T. Following an MPRAGE anatomical scan, T2*-weighted BOLD data (2.2 mm isotropic) were acquired using 3-echo (TR = 1900 ms; TEs = 11, 21, 32 ms), 5-echo (TR = 2800 ms; TEs = 11, 21, 32, 43, 54 ms), and 7-echo (TR = 3700 ms; TEs = 11, 21, 32, 43, 54, 65, 76 ms) sequences. A high-resolution 3-echo variant (1.7 mm isotropic; TEs = 18, 48, 78 ms) was also collected. Data were preprocessed via AFNI and denoised with Tedana. Whole-brain tSNR was calculated, and resting-state functional connectivity (rsFC) was assessed via Pearson correlations using a Default Mode Network (DMN) seed. Resultant maps were clustered (>50 voxels) and evaluated for group agreement using the Dice coefficient. **Results:** Three-echo acquisitions showed an over two-fold whole-brain tSNR advantage compared to SE, particularly in frontal and occipital lobes. DMN-to-whole-brain rsFC maps from ME data revealed more specific, higher-threshold functional connections and clusters with greater group agreement (Dice coefficient) than SE data. Enhanced sensitivity enabled high-resolution acquisition (1.7 mm isotropic) while maintaining a high whole-brain average tSNR of 93.5 **Conclusion/implications:** HPHG ME-fMRI increases the sensitivity and reliability of resting-state functional brain mapping. By mitigating susceptibility artifacts and blurring in susceptibility prone brain regions, this approach strengthens the utility of rs-fMRI for clinical neuroradiological examinations.

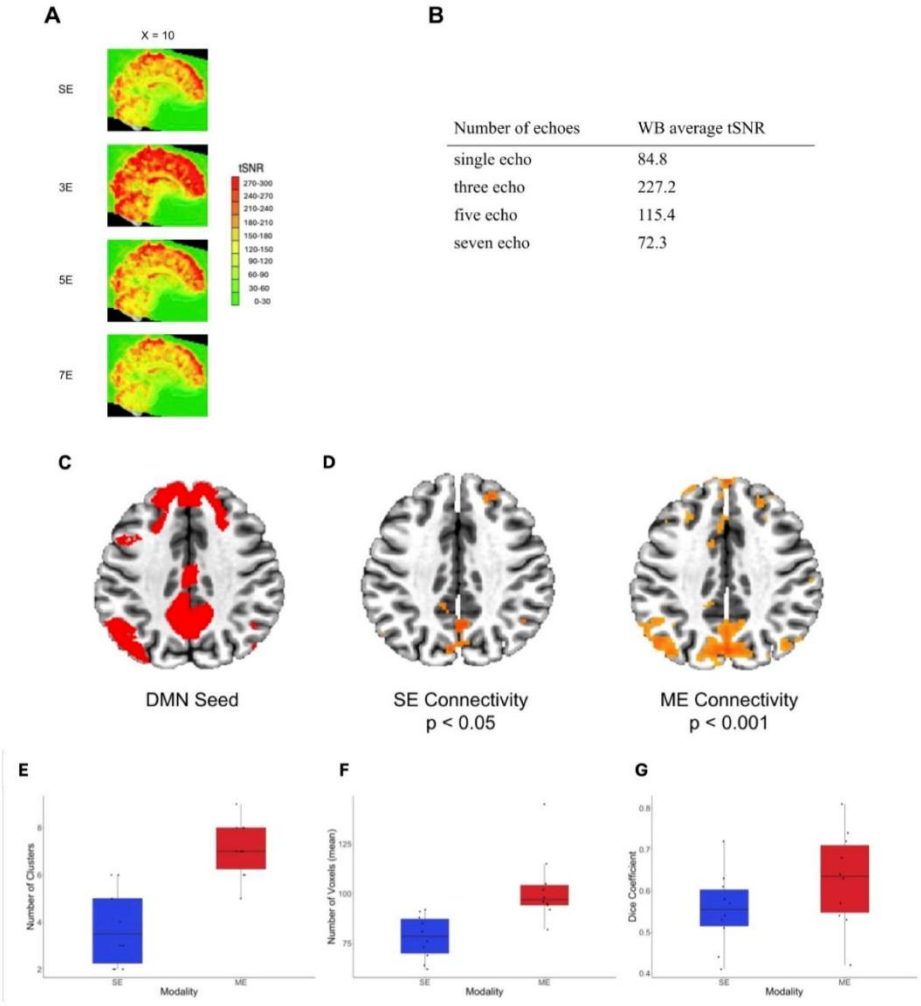


Figure 1: (A) Sagittal view of tSNR for SE and ME acquisitions for a representative subject. (B) Average tSNR in whole brain for SE and ME acquisitions. The 3-echo and 5-echo ME acquisitions have significantly improved ($p < 0.05$) tSNR compared to SE. The 7-echo protocol has lower tSNR due to signal decay in the sixth and seventh echo. (C) The default mode network seed used for functional connectivity analysis was extracted from a highly cited resting state atlas (Yeo et al. 2011). (D) Maps for group average seed-based correlation analysis after denoising and functional connectivity estimation. SE connectivity map was thresholded to $p < 0.05$ and ME connectivity map was thresholded to $p < 0.001$. (E) Number of clusters greater than 50 voxels identified in optimized multi-echo (ME) 3-echo protocol versus single-echo (SE) acquisitions. (F) Average number of voxels for clusters identified. (G) DICE coefficient of individual identified clusters compared to group average.

Disclosures: J. Shao: None. **K. Soderlund:** None. **C. Vojta:** None. **T. Yuan:** None. **H.D. Morris:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.18/FF28

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant ZIAMH002783

Title: Nonlinear warp fields reveal physiological and task-related brain morphometry dynamics in fMRI

Authors: *B. AKIN[1], T. MORGAN[2], S. I. KRONEMER[2], D. A. HANDWERKER[3], P. BANDETTINI[2];
[1]NIH, Natl. Inst. of Mental Hlth. (NIMH), Bethesda, MD; [2]Section on Functional Imaging Methods, [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Nonlinear image registration is widely used in structural MRI and high-resolution laminar fMRI studies to achieve submillimeter anatomical alignment. In conventional fMRI, however, nonlinear deformation fields are rarely estimated at each time point and are generally used for motion correction or denoising. Here, we investigate whether voxelwise nonlinear warp fields derived from standard-resolution (2-3 mm) fMRI time series can reveal physiologically meaningful morphological changes throughout the living human brain.Using nonlinear registration applied to conventional and ultrafast fMRI datasets, we estimated voxelwise deformation fields for every image volume and extracted measures of local displacement and tissue expansion or contraction. Temporal spectral analysis of the resulting warp time series was used to identify physiological and task-related dynamics. We also examined warp-field responses during respiratory challenge paradigms consisting of repeated inhale-and-hold and exhale-and-hold tasks.Preliminary results demonstrate anatomically specific deformation patterns throughout the brain. Warp-derived signals reveal expansions and contractions of ventricular structures, motion of vascular compartments, and deformation of cortical and periventricular regions. Spectral analyses show distinct spatial distributions associated with respiratory and cardiac pulsations, while task-related frequencies are detectable in selected cortical areas.Respiratory challenge tasks produced markedly different deformation patterns. Inhale-and-hold periods were associated with prominent responses within deep white matter regions, whereas exhale-and-hold periods produced stronger responses in insular and periventricular areas and regions adjacent to the ventricular system. These differences suggest that respiratory state influences brain morphology through distinct vascular, cerebrospinal fluid, and tissue-compartment dynamics.These findings suggest that nonlinear warp fields contain structured biological information beyond their traditional role in image alignment. Rather than serving solely as preprocessing intermediates, time-resolved deformation fields may provide a framework for studying brain biomechanics, neurovascular coupling, cerebrospinal fluid dynamics, and physiological regulation using existing fMRI datasets. Ongoing work relates these deformation dynamics to concurrent measurements of blood pressure, vascular tone, and low-frequency photoplethysmography fluctuations to better understand the systemic physiological processes underlying observed brain deformations.

Disclosures: B. Akin: None. **T. Morgan:** None. **S.I. Kronemer:** None. **D.A. Handwerker:** None. **P. Bandettini:** None.

Poster

PSTR067: Functional Imaging and Brain Connectivity

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR067.19/FF29

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CDMRP HU00012020057

Title: Stage-Dependent Microarousal Coupling to Prefrontal Water Flux: An fNIRS Window into Human Glymphatic Dynamics

Authors: *S. SEENIVASAN;
Uniformed Services Univ., Bethesda, MD

Abstract: Background: Microarousals (MAs) are proposed markers of noradrenergic-driven glymphatic cycling during NREM sleep, with recent rodent work demonstrating that norepinephrine-mediated vasomotion drives glymphatic clearance time-locked to these events. Yet standard AASM arousal scoring conflates spontaneous noradrenergic MAs with respiratory arousals that may disrupt rather than support clearance — obscuring their functional heterogeneity. This exploratory study tested whether sleep stage and respiratory context modulate MA coupling to prefrontal water flux in humans.
Methods: Nine adults (mean age 42y, 78% male, median AHI 3) contributed 13 overnight polysomnography and functional near-infrared spectroscopy (fNIRS) recordings. fNIRS measured prefrontal water concentration dynamics as a noninvasive proxy for glymphatic transport. MAs were manually scored per AASM criteria and classified as spontaneous or apneic (within ±10s of a scored apnea/hypopnea). Spearman correlations were computed between per-stage MA counts and mean stage water flux.
Findings: Pooled MA counts showed no relationship with water flux ($\rho=0.06$, $p=0.85$). Stage stratification revealed a biphasic pattern: N2 MAs correlated positively ($\rho=0.64$, $p=0.022$), while N3 trended negative ($\rho=-0.39$, $p=0.19$). Apneic MA removal preserved the N2 coupling ($\rho=0.66$, $p=0.014$) while collapsing the N3 trend to null ($\rho=-0.06$, $p=0.86$), implicating respiratory MAs specifically as disruptors of deep-sleep clearance.
Conclusions: MA-flux coupling is stage-dependent and sensitive to respiratory context. Spontaneous N2 MAs appear functionally coupled to glymphatic water dynamics, consistent with noradrenergic gating of perivascular fluid transport. Apneic MAs selectively disrupt N3 clearance. These findings challenge the clinical goal of arousal suppression and motivate a phenotype-based reclassification of MAs as a biomarker of glymphatic function.

Disclosures: S. Seenivasan: None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.01/FF30

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R35GM151020

Title: Circadian regulation of the locus coeruleus-medial prefrontal cortex pathway underlies spontaneous homecage behavior

Authors: *S. O. SWECK[1], J. R. JONES[2];
[2]Biol., [1]Texas A&M Univ., College Station, TX

Abstract: In the brain, circadian rhythms are generated by molecular clocks that regulate physiology and behavior across the 24-hour cycle. While these rhythms are well-characterized in simple behaviors such as locomotion and feeding, their influence on neural circuits supporting complex, spontaneous behavior remains poorly understood. The locus coeruleus (LC) and medial prefrontal cortex (mPFC) form a circuit that plays a key role in executive control and behavioral organization during spontaneous homecage behavior, yet it is unknown whether this network undergoes circadian modulation. We hypothesized that intrinsic molecular clocks within the LC contribute to circadian regulation of LC-mPFC circuit dynamics and the temporal organization of spontaneous behavior. To test this, we recorded calcium activity in LC noradrenergic terminals in the mPFC using long-term fiber photometry in freely behaving mice across light-dark and constant-darkness conditions. We found that LC-mPFC projection activity exhibits robust ~24-hour rhythms that persist in constant darkness and peak in early- to mid-subjective day, demonstrating endogenous circadian regulation of this pathway. To determine whether LC molecular clocks contribute to circadian circuit function and behavioral organization, we selectively disrupted BMAL1 in LC noradrenergic neurons using CRISPR/Cas9-mediated gene editing. We then performed long-term recordings of LC-mPFC activity and quantified nine spontaneous homecage behaviors using our machine learning-based behavioral classification pipeline. LC clock disruption reduced circadian rhythm strength in 8 of 9 behaviors and produced a loss of temporal organization across the daily cycle, indicating that molecular clocks within LC neurons contribute to the structuring of spontaneous behavior. Together, these findings identify the LC as a source of circadian regulation within the LC-mPFC pathway and demonstrate the LC molecular clocks contribute to the temporal organization of spontaneous behavior. Altogether, these experiments provide a framework for understanding how circadian dysfunction may disrupt the organization of daily behavior in neuropsychiatric disorders characterized by impaired executive function and circadian disturbance.

Disclosures: S.O. Sweck: None. **J.R. Jones:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.02/FF31

Topic: G.07. Biological Rhythms and Sleep

Title: Cholinergic signaling as a conduit for circadian modulation of hippocampal circuits

Authors: *F. MOHAMMADPOURMIR[1], J. R. JONES[2];
[2]Biol., [1]Texas A&M Univ., College Station, TX

Abstract: Circadian rhythms in behavior are synchronized by the brain's central circadian pacemaker, the suprachiasmatic nucleus (SCN). More complex behaviors, such as learning and memory, also exhibit daily rhythms coordinated by the SCN and local clocks, and these rhythms fragment with circadian disruption. However, the circuit-level pathways through which the SCN influences memory-related brain regions remain poorly understood. Because the hippocampus receives little to no direct input from the SCN, circadian regulation is likely conveyed through intermediate structures. One potential relay is the medial septum of the basal forebrain, which sends extensive cholinergic projections to the hippocampus and modulates hippocampal network dynamics underlying learning and memory. Consistent with this role, our prior data show that the medial septum receives direct neuronal input from the SCN, positioning it to transmit circadian timing cues to the hippocampal circuit via acetylcholine. Here, we tested the hypothesis that circadian timing regulates hippocampal function by modulating the temporal dynamics of acetylcholine release. To assess whether hippocampal ACh release is endogenously rhythmic, we expressed a genetically encoded ACh sensor in the CA1 layer of the hippocampus of wild-type mice and performed continuous long-term fiber photometry recordings over 10 days. We found that ACh release exhibits a robust time-of-day-dependent rhythm, with higher levels during the inactive phase. This rhythm persisted under constant darkness, indicating that it is generated by an internal circadian mechanism rather than by external light cues. These results suggest that hippocampal acetylcholine release is under endogenous circadian control, supporting a model in which cholinergic signaling provides a temporally structured conduit for circadian modulation of hippocampal function.

Disclosures: F. Mohammadpourmir: None. **J.R. Jones:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.03/FF32

Topic: G.07. Biological Rhythms and Sleep

Support: Whitehall Foundation
NIH R35GM151020
NIH F31DA065512-01

Title: Antiphasic Circadian Rhythms in Dopamine Release Tune Reward Signaling

Authors: *J. COOK[1], N. KEENE[2], J. R. JONES[3];
[1]Texas A&M Univ. Neurosci. Inst. For Neurosci., College Station, TX; [3]Biol., [2]Texas A&M Univ., College Station, TX

Abstract: The circadian system is an essential regulator of reward-related neural function and behavior.Through proper timing of biological activity, the circadian system promotes survival by calibrating when animals seek out rewards such as food sources, mates, and safety. The release of dopamine (DA) into the nucleus accumbens (NAc) is critical for driving reward behaviors. However, how circadian modulation of DA release shapes reward signaling and behavior remains unknown. Here, I hypothesized that rhythms in DA release drive rhythms in reward behavior. Using long-term fiber photometry combined with an automated reward delivery and measurement system, I directly investigated the relationship between DA release and reward behavior on a circadian timescale. My results revealed two distinct circadian rhythms in DA release: basal, reflecting bulk changes in spontaneous DA release, and reward-evoked, reflecting transient changes in DA release tied to reward behavior. I specifically uncovered that basal DA release peaks during the morning, antiphase to that of reward-evoked DA release, which peaks during the early night and is in phase with reward behavior. I further discovered a statistically significant relationship between basal and reward-evoked DA release, such that lower levels of basal DA release correlate to greater reward-evoked DA signaling. Reward-evoked DA release also positively correlates with reward behavior, with greater DA signaling occurring at night. Taken together, these results suggest that circadian control of DA release operates through a signal-tuning mechanism in which basal DA " noise" is suppressed during ethologically relevant times of day to amplify reward-evoked DA signals. More broadly, this work identifies signal tuning as a general strategy by which the circadian system modulates neural circuit activity to generate rhythms in behavior.

Disclosures: J. Cook: None. **N. Keene:** None. **J.R. Jones:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.04/GG1

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R01NS118856
NIH Grant R01NS073613
NIH Grant R01NS091126

Title: Circadian gating of torpor entry reveals a clock-dependent threshold for hypometabolic state transitions

Authors: *M. S. ALARCON[1], F. ASANO[2], E. ARRIGONI[3], P. M. FULLER[4];
[1]Neurolog. Surgery, Univ. of California, Davis, Davis, CA; [2]Dept. of Neurolog. Surgery, Univ. of California Davis, Davis, CA; [3]Neurol., BIDMC and Harvard Med. Sch., Boston, MA; [4]U.C. Davis Sch. of Med., DAVIS, CA

Abstract: Torpor is a highly conserved physiological adaptation that enables animals to survive periods of energetic challenge by entering a regulated hypometabolic state characterized by reductions in body temperature (Tb), metabolic rate, and neural activity. Although the physiological features of torpor have been extensively characterized, the mechanisms that determine when animals enter torpor remain poorly understood. We hypothesized that torpor entry is regulated by an endogenous circadian gating mechanism that determines when metabolic signals are permitted to trigger the transition into torpor. To test this hypothesis, mice were housed under free-running conditions in constant darkness (DD) and subjected to a single 24-hour fasting period initiated at different circadian phases. Continuous EEG and Tb recordings were obtained to identify torpor onset and characterize associated physiological state transitions. Food-restricted mice exhibited torpor bouts that clustered within a defined circadian window regardless of whether fasting was initiated at circadian time (CT) 0 or CT12. These findings indicate that torpor entry is not determined solely by the duration of food deprivation, but instead occurs within a restricted circadian phase during which metabolic challenge can trigger entry into a hypometabolic state. Together, these results support a model in which torpor represents a circadian-gated threshold-crossing event arising from the interaction between metabolic drive and endogenous clock signals. Ongoing studies are testing whether a genetically defined population of neurons within the suprachiasmatic nucleus contributes to the generation of this permissive circadian gate and thereby regulates the timing of torpor entry.

Disclosures: M.S. Alarcon: None. **F. Asano:** None. **E. Arrigoni:** None. **P.M. Fuller:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.05/GG2

Topic: G.07. Biological Rhythms and Sleep

Title: Nicotine anticipatory behavior exhibits an ovarian hormone-dependent infradian rhythm in female mice

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Abstract: Sex differences in nicotine addiction have been associated with ovarian hormone fluctuations. However, the impact of these hormonal shifts on anticipatory responses to repeated nicotine exposure remains unclear. This study investigated whether chronic nicotine administration interacts with the estrous cycle to modulate anticipatory locomotor activity. Adult female C57BL/6 mice were assigned to four groups (n=6): intact-water, intact-nicotine, ovariectomized (OVX)-water, and ovariectomized (OVX)-nicotine. During 14 consecutive days, animals received either nicotine (3 mg/mL) or water nebulization at ZT4 (light/dark cycle 12:12). Nicotine anticipatory activity was quantified as wheel-running behavior during the 2-h interval preceding daily nebulization. Estrous cycle stages were determined by vaginal cytology throughout the experiment. Intact nicotine-treated females displayed a recurrent increase in anticipatory activity with an approximate 4-5-day periodicity, establishing a clear drug-induced infradian rhythm. Analysis across the cycle phases revealed significantly greater nicotine anticipatory activity during receptive phases (proestrus and estrus) than non-receptive phases (metestrus and diestrus). Interestingly, this rhythmic pattern of anticipation was completely absent in both ovariectomized nicotine-treated and water-treated mice. Beyond modulating behavior, chronic nicotine exposure altered homeostatic estrous cycle organization, significantly lengthening the duration of metestrus during the second week of treatment. These findings suggest that ovarian hormones modulate the temporal expression of nicotine anticipatory behavior. Repeated nicotine administration reveals an infradian locomotor rhythm tightly aligned with the estrous cycle, highlighting a novel interaction between reproductive physiology and the chronobiological mechanisms underlying drug-anticipation.

Disclosures: C.J. Juárez-Portilla: None. **Z.M. Rosas:** None. **R.C. Zepeda:** None. **G. Aguirre:** None. **T. Molina-jimenez:** None. **A.A. Corona-Morales:** None. **R.C. Salgado-Delgado:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.06/GG3

Topic: G.07. Biological Rhythms and Sleep

Support: Department of Anesthesiology, University of Michigan Medical School
Undergraduate Research Opportunity Program, University of Michigan

Title: Intravenous administration of 2,5-Dimethoxy-4-Iodoamphetamine, a serotonergic psychedelic, decreased the sensitivity to general anesthesia in rats

Authors: *A. RAGHU[1], M. HE[2], E. HUELS[1], T. LIU[1], D. PAL[1];
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Abstract: Although serotonergic psychedelics are being actively studied for their therapeutic potential to treat mental health disorders, an understudied property of these agents is the ability to increase wakefulness and promote a neurophysiological profile consistent with an activated brain state. In a recent study, we showed that intravenous delivery of 2,5-Dimethoxy-4-Iodoamphetamine (DOI), a classic serotonergic psychedelic, can induce behavioral arousal and reverse general anesthesia despite the continued delivery of anesthetics (propofol or isoflurane). While these data show that DOI delivery during anesthesia can induce behavioral arousal, it is unknown whether DOI administered during normal wakefulness will prime the brain to oppose a state change induced by anesthetics. Therefore, in this study, we determined the effect of intravenous delivery of DOI on the time to loss of righting reflex (LORR), a surrogate for loss of consciousness in rodents, after isoflurane or propofol anesthesia. In addition, we quantified the time to return of righting reflex (RORR) and the changes in EEG spectral power and corticocortical coherence. Adult Sprague-Dawley rats (n=6 males, 6 females) were surgically implanted with electrodes to record EEG across cortex and a chronic catheter in jugular vein for delivery of propofol and DOI. After 20 minutes of EEG recording during normal wakefulness, the animals received a bolus of either 0.5 mg/kg DOI or 0.9% saline (vehicle control) over one minute. Ten minutes later, the animals were anesthetized with either 1.3% isoflurane or 1 mg/kg/min propofol infusion, and the time to LORR was measured. After the LORR, propofol was down-titrated to 0.65 mg/kg/min whereas isoflurane continued at the same concentration (1.3%). After a total of 40 minutes of anesthesia, the anesthetic delivery was stopped and the time to RORR was measured. Data show that DOI increased the time to LORR (DOI 513.14 + 115.29 seconds, saline 441.65 + 93.45 seconds), reduced the time to RORR (DOI 282.14 + 21.85 seconds, saline 419.83 + 35.85 seconds). Preliminary analyses suggest increased medium (65-115 Hz) and high gamma (125- 165 Hz) corticocortical coherence after DOI infusion and before, during and after anesthesia. These data validate the previous reports, including from our group, of the arousal-promoting effect of psychedelics and motivate studies aimed at the exploration of psychedelics to reverse depressed states of consciousness.

Disclosures: A. Raghu: None. **M. He:** None. **E. Huels:** None. **T. Liu:** None. **D. Pal:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.07/GG4

Topic: G.07. Biological Rhythms and Sleep

Support: NINDS R01NS121161

Title: A clock in the motor cortex (M1) regulates $Ca^{+2}$and locomotor behavior robustness

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Abstract: Circadian clocks regulate daily behaviors like sleep and locomotion, but little is known about how the primary motor cortex (M1) participates in circadian regulation of motor behaviors. To determine if neuronal activity in M1 changes with time of day, we used in vivo fiber photometry to record cell-type-specific calcium fluorescence in layer 5 (L5) of M1 neurons from freely moving C57 mice. We measured calcium events (e.g. peak heights and integrated intensity) for 10 min every hour over multiple days in mice injected with AAV8 Syn-GCaMP8m and implanted with a fiber optic in L5. M1 neurons showed daily rhythms (Metacycle, $p<0.001$) in calcium events under a 7am:7pm light:dark cycle, peaking in the early night (ZT 14.7 ± SEM, n=7 mice; Rayleigh test, $P<0.0001$). These rhythms persisted in constant darkness with a period of 23.8 h ± SEM, n=7 mice). In contrast, control mice injected with AAV8 Syn-EGFP in L5 did not show daily rhythms in fluorescence. We next test if M1 neurons require the core circadian clock gene, Bmal1, to control daily rhythms in motor behavior and M1 Ca^{2+}. We injected AAV8 Syn-Cre tdTomato or Syn-m-cherry bilaterally into M1 of $Bmal1^{fl/fl}$ mice and found that, compared to controls, ablation of Bmal1 in M1 neurons reduced the amplitude and anticipation of daily rhythms in Ca^{2+} (t-test, $p<0.05$) and locomotion (t-test, $p<0.01$). We conclude that a circadian clock in M1 neurons entrains to local time and promotes daily increases in neuronal activity and rest-wake behavior.

Disclosures: D. Granados-Fuentes: None. **E.D. Herzog:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.08/GG5

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R01CA270372

Title: Pharmacological circadian synchronization via CK1 ε/δ inhibition as an intervention to reduce chemotherapy-induced fatigue in mice

Authors: *G. C. WINSTEL[1,2,3], Z. M. TAPP[2], A. MAIBACH[2], M. M. SENG[2], K. H. OBRIETAN[3], L. M. PYTER[2,4];
[1]The Ohio State University, Neurosci. Grad. Program, Columbus, OH; [2]Inst. of Brain, Behavior and Immunol., [3]Neurosci., [4]Psychiatry and Behavioral Hlth., The Ohio State Univ., Columbus, OH

Abstract: Chemotherapy causes many side effects— some of which are mediated by the central nervous system. Fatigue is a complex and persistent side effect of chemotherapy that significantly reduces quality of life for patients and is hypothesized to be partly centrally mediated. Circadian disruption is observed in humans and mice receiving chemotherapy and has been correlated with fatigue severity. However, chemotherapy-induced fatigue and circadian disruption have not been causally linked. Our lab has previously reported that chemotherapy

disrupts circadian rhythms of a principal oscillator (the suprachiasmatic nuclei of the hypothalamus) in mice. Chemotherapy-induced fatigue, measured by running wheel activity, is also more severe when circadian timing cues are removed (constant darkness; DD), indicating that circadian desynchrony might causally exacerbate fatigue severity. We aimed to resynchronize circadian rhythmicity in mice receiving chemotherapy by administering a drug that inhibits casein kinase 1 (CK1) ε/δ, a regulatory component of the molecular clock signaling pathway. We hypothesized that this pharmacological circadian resynchronization reduces chemotherapy-induced fatigue. To study this, female 9-week-old C57BL/6 mice were singly housed with running wheels and entrained to a 12:12 light-dark (LD) cycle or held in DD conditions to measure endogenous rhythmicity of wheel-running activity. After acclimation and baseline activity data collection, mice received paclitaxel chemotherapy (30 mg/kg) or vehicle i.p. injections every other day for six doses. On the first day of injections, mice also began receiving once daily i.p. injections of PF-670462 (CK1 inhibitor; 30 mg/kg) or control for a total of 25 doses, resulting in a 2x2 design with four treatment groups. Chemotherapy reduced daily number of wheel revolutions, regardless of the CK1 inhibitor or control treatment for LD and DD groups. The CK1 inhibitor did not rescue this fatigue, nor did it accelerate recovery from chemotherapy compared to controls. Further circadian rhythm analyses of daily wheel running are ongoing to validate the efficacy of the CK1 inhibitor on resynchronizing activity rhythms. However, at this time, we cannot reasonably conclude that chemotherapy-induced circadian disruption is causing physical fatigue in our mouse model. Further work is needed to identify the mechanisms by which chemotherapy may be contributing to fatigue and how circadian rhythm disruption may be influencing fatigue severity.

Disclosures: G.C. Winstel: None. **Z.M. Tapp:** None. **A. Maibach:** None. **M.M. Seng:** None. **K.H. Obrietan:** None. **L.M. Pyter:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.09/GG6

Topic: G.07. Biological Rhythms and Sleep

Support: BGSU Building Strength Grant

Title: Glioma cells generate large extracellular vesicles expressing CD47, a circadian clock-regulated protein that suppresses cancer cell removal

Authors: S. AFRIN, *M. E. GEUSZ;
Dept. of Biol. Sci., Bowling Green State Univ., Bowling Green, OH

Abstract: Cancer cells generate large extracellular vesicles (LEVs) that carry information through microRNA and other molecules to non-cancer cells in the tumor environment thereby suppressing immunodetection of the cancer cells and their removal through phagocytosis. The

transmembrane protein CD47 found in many types of cells binds receptors of macrophages and microglia to suppress phagocytosis, and cancer cells are protected by their elevated CD47 levels. CD47 gene expression is regulated by the circadian clock suggesting that multiple CD47 functions may be timed to coordinate with daily rhythms in immune cell behavior, possibly providing protection at a phase of the cycle when phagocytes are known to be most active. It remains unclear whether LEV actions in the tumor microenvironment are also modulated by the circadian clock, which is likely if CD47 protein is present and functional in LEVs. Immunotherapy methods that deliver anti-CD47 antibodies to cancer patients are being refined to better target cancer cells and could benefit from the exploration of CD47-positive LEVs and circadian timing. CD47 has been detected in small extracellular vesicles, the exosomes. To evaluate CD47 in LEVs produced from glioma cells we tested the rat C6 cell line that has provided insights into the relationship between circadian rhythms and glioblastomas. The LEVs examined were fixed with methanol on glass-bottom culture dishes. Three versions of the monoclonal antibody MIAP410 and confocal microscopy revealed CD47 occurring in clusters on live and fixed cells, as previously reported, and on vesicles scattered across the glass in the presence or absence of fetal bovine serum. The diameter range of the vesicles when examined through immunofluorescence (IF) was 1.8 to 2.1 microns, which is within the 1 to 10-micron range reported for oncosomes, LEVs specifically released from cancer cells. IF also identified annexin A2 that was widely distributed across the LEVs and cell bodies indicating the vesicles were generated from membrane blebbing rather than as multivesicular bodies. LEVs are also formed from cells undergoing apoptosis, but the lack of LEV immunofluorescence for calcium-binding protein calreticulin (CALR) and the cell morphology indicated apoptotic cells were not the source. Cell-surface CALR stimulates phagocytosis and was present in the fixed and unfixed cells agreeing with its elevated presence in cancer cells and cancer stem cells where it regulates phagocytosis rate according to the CALR/CD47 ratio. Further exploration of glioma-derived LEVs will likely reveal additional roles for circadian clock-controlled CD47 in tumor cell communication.

Disclosures: S. Afrin: A. Employment/Salary (full or part-time):; Bowling Green State University. **M.E. Geusz:** A. Employment/Salary (full or part-time):; Bowling Green State University.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.10/GG7

Topic: G.07. Biological Rhythms and Sleep

Title: Brain changes induced by cancer-associated sleep disruption

Authors: *C. HUNG[1], A. M. GOMEZ[2], J. C. BORNIGER[3];
[1]cold spring harbor lab, COLD SPRING HARBOR, NY; [3]Neuroscience/Cancer Ctr., [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Sleep disturbance is one of the most common symptoms reported by cancer patients, yet the mechanisms linking tumor burden to disrupted sleep remain poorly understood. Clinical studies indicate that disturbed sleep affects more than one quarter of cancer patients. Importantly, cancer-associated sleep disturbance is not fully explained by hormone levels, surgery, or chemotherapy, suggesting that the tumor itself may directly or indirectly alter sleep-regulatory brain function.To model cancer-associated sleep disruption, we examined sleep-wake architecture during tumor development using two mouse models: an orthotopic EO771 breast cancer model in female mice and a B16 melanoma model in male mice. One week after EO771 tumor inoculation, during an early stage of tumor growth, mice showed increased fragmentation of sleep-wake behavior. In contrast, the B16 melanoma model showed an opposite phenotype, with increased sleep after tumor inoculation. In addition to sleep and wakefulness, we also assessed changes in natural home-cage behavior during tumor progression. We found that the timing of consummatory behavior was shifted from the active dark phase toward the normally inactive light phase.To investigate how cancer alters brain function related to sleep, we compared whole-brain neuronal activity under sleep stress conditions in healthy and tumor-bearing mice. Neuronal activity was assessed using c-Fos, an immediate early gene marker of neuronal activation. c-Fos mapping revealed a broadly activated brain state following sleep deprivation in tumor-bearing mice. Among all brain regions examined, areas surrounding the third ventricle showed particularly strong increases in neuronal activity. These regions are enriched in excitatory neurons and project to several sleep-wake regulatory areas, including the lateral hypothalamus and periaqueductal gray. Further neuronal activity and the functional role of these neurons during cancer will be discussed in this presentation.

Disclosures: C. Hung: None. **A.M. Gomez:** None. **J.C. Borniger:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.11/GG8

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R35 GM127102

Title: Flashing light modulates insect behavior in a species-specific manner

Authors: *M. S. ALI[1], X. LUO[1], D. D. AU[1,3], T. C. HOLMES[1,2];
[2]Ctr. for Neural Circuit Mapping, [1]Univ. of California, Irvine, Irvine, CA; [3]Dept. of Neurobio., Stanford Univ., Stanford, CA

Abstract: Artificial light differs from natural illumination by exhibiting temporal flicker across a wide range of frequencies. Although insect responses to light have been studied primarily in the context of phototaxis and flicker fusion thresholds, how temporal light structure beyond perceptual limits influences behavior remains poorly understood. We developed a programmable

flashing light system (FLASH: Flickering Light of Actuatable Spectral Hues) to investigate frequency-dependent behavioral responses across multiple Drosophila species. Rhythmic light stimulation evokes robust, frequency-specific, and species-specific photo-preference behaviors at temporal frequencies exceeding known flicker perception thresholds. FLASH stimulation also alters time-of-day-organized behavioral patterns, suggesting structural disruption of circadian-regulated behavioral output. Genetic and circuit analyses in Drosophila melanogaster demonstrates that FLASH-evoked behaviors require coordinated activity of canonical visual phototransduction pathways and non-image-forming photoreceptors, including Cryptochrome and Rhodopsin-7. Disruption of circadian clock function or synaptic input from lateral ventral clock neurons abolishes FLASH-induced behavioral responses, indicating dependence on central circadian circuitry. Together, these findings demonstrate that temporal structure of light modulates insect behavior through integrated visual and circadian pathways. These results provide a framework for understanding rhythmic environmental light signaling and for designing species-specific light-based strategies to control insect behavior.

Disclosures: M.S. Ali: None. **X. Luo:** None. **D.D. Au:** None. **T.C. Holmes:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.12/GG9

Topic: G.07. Biological Rhythms and Sleep

Support: HHMI

Title: Light-induced immediate early gene (IEG) expression in Drosophila circadian neurons

Authors: *M. IVANOVA[1], G. BERGLUND[2], P. OJHA[1], M. ROSBASH[3];
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Abstract: Circadian behaviors are driven by rhythmic gene expression within clock neurons, but how these molecular programs interact with light and neural activity and contribute to circadian functions remains incompletely understood. Also incompletely understood is immediate early gene (IEG) expression within these neurons. These genes are induced by neuronal activity and function as key regulators of downstream transcriptional programs, making them strong candidates for linking neuronal activity to circadian gene expression and behavior. We have shown that IEGs are also rapidly induced by neuronal activity within the clock neurons, but this work was done prior to the single cell RNA-Seq characterization of *Drosophila* circadian neurons, so it is not known which genes are expressed in which of the many circadian neuron subtypes. Moreover, the relationship of IEG expression to light and cryptochrome as well as to the circadian regulation of neuronal activity (in constant darkness) is unknown. To address some of these issues, we have used nuclear single cell-Seq to identify multiple IEGs that are

selectively induced in distinct circadian neuron subtypes in response to light. Notably, some of the most prominent IEGs are preferentially expressed in morning cells following lights-on, and very surprisingly these same IEGs are expressed in evening cells following lights-off. These findings were validated using RNA in situ hybridization. Together, our results reveal cell-type-specific, light-dependent induction of IEGs within the circadian circuit. Ongoing work is focused on determining how IEG activation influences circadian behavioral rhythms and on identifying the molecular pathways controlling this activation, including which IEGs and which specific circadian neuron populations are most important to behavior. Details of the light activation pathway as well as the role of cryptochrome in IEG activation are on our short-term radar screen.

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Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.13/GG10

Topic: G.07. Biological Rhythms and Sleep

Support: NSF Award #2235711

Title: Endogenous circadian rhythm collapses as light entrainment strengthens during black widow spider (Latrodectus mactans) development: a combined behavioral and modeling study

Authors: *N. TOPORIKOVA[1], D. ROBB[2], N. AYOUB[1];
[1]Washington and Lee Univ., Lexington, VA; [2]Roanoke Col., Salem, VA

Abstract: Circadian behavior is built on two functionally separable components: an endogenous oscillator and an entrainment pathway that couples it to light. Whether these mature in parallel or independently during postembryonic development is unknown for most invertebrates. We tracked locomotor activity in a longitudinal cohort of black widow spiders (Latrodectus; n = 31, 30, 31, 9 at 2, 4, 6, 9 months of age) under both LD 12:12 and constant darkness (DD), recorded at 1-min resolution with infrared activity monitors. Per spider we computed Lomb-Scargle (LS) peak prominence (peak/mean band power), phase angle of entrainment, activity-weighted circular statistics, bout duration distributions, within-bout intensity, and bout-onset clock-gating across the cycle. Light-entrained rhythmicity strengthened with age: LS prominence at 24 h rose from 1.75 ± 0.12 to 5.81 ± 0.19 (mean ± SEM; Kruskal-Wallis (KW) $p \approx 1\times10^{-10}$), rhythmic spiders rose from 0% to 100% (χ^2 $p \approx 1\times10^{-10}$), and phase precision tightened from 1.14 to 0.17 h SD. In striking contrast, free-running rhythmicity weakened: DD LS prominence at the individual free-running period fell from 5.02 ± 0.31 to 2.76 ± 0.19 (KW $p \approx 1\times10^{-3}$), and rhythmic spiders fell from 97% to 25%. Bout duration was age-invariant in both conditions (KW p = 0.58 LD, 0.98 DD), confirming a stable locomotor central pattern generator (CPG). Within-bout intensity grew ~3-fold in both conditions ($p < 1\times10^{-10}$), consistent with motor-output gain maturation independent of clock state. Bout-onset clock-gating was age-invariant under LD (p =

0.24) but declined sharply under DD ($p \approx 1\times10^{-4}$), implicating clock-to-locomotor coupling rather than direct light masking as the developmentally changing component. To distinguish among candidate mechanisms (photoreceptor maturation, clock-amplitude decline, clock-output coupling weakening, masking modulation, motor-gain growth) we developed a mathematical model in which a Goodwin-type circadian oscillator drives a locomotor compartment via parallel entrainment and masking pathways; age-dependent parameter fits will rank competing hypotheses against LD, DD, and bout-level data. The paradoxical inversion (entrained behavior strengthens while the free-running oscillator weakens) challenges the assumption that entrainment and endogenous oscillation co-mature, identifies clock-output coupling as a tractable site of developmental change in arthropod circadian behavior, and provides a framework for studying clock-locomotor maturation in animals where longitudinal neural recording remains intractable.

Disclosures: N. Toporikova: None. **D. Robb:** None. **N. Ayoub:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.14/GG11

Topic: G.07. Biological Rhythms and Sleep

Support: Pritzker Neuropsychiatric Research Grant

Title: Digital phenotyping reveals differing circadian behavior in selectively bred high and low responder Sprague-Daly Rats

Authors: *D. KIM[1], A. GREEN[2], A. JOHNSON[1], A. GHIMIRE[3], E. K. HEBDA-BAUER[4], P. M. MARAS[4], H. AKIL[4], B. O. WATSON[5];
[1]Biomed. Engin., [2]Univ. of Michigan Med. Sch., [3]Neurosci., [4]Michigan Neurosci. Inst., [5]Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI

Abstract: Here, we explore a digital phenotyping approach in rodents to more quantitatively measure the effects of chronic stress as a model for Major Depressive Disorder (MDD). MDD is a prevalent psychiatric illness that is largely diagnosed through self-reporting of long-term behavior. Because the symptoms in MDD patients permeate into the activities of daily living (eating, sleeping, motivation, others), digital phenotyping is a promising approach for continuous behavioral data acquisition that has recently been applied to evaluating psychiatric disorders like MDD. Another method to understand MDD is to use rodent neuroscience, where powerful brain-probing tools are regularly used. These models are valued in psychiatric research due to their reliable reproduction of translatable depressive-like symptoms in response to stress; however, most rodent chronic stress measurement efforts have historically been based on short-duration assays such as the tail suspension test that can be difficult to translate to humans. This is due to the rather arbitrary and short-term nature of the laboratory tests, which contrast with the changes

in activities of daily living in MDD that can be measured with digital phenotyping. The digital homecage (DHC) we developed for rats can bridge this gap to better reveal the effects of stress in translatable behavioral domains (eating, sleep, energy, motivation). An important factor in studying stress/MDD is that individual differences in temperament have been associated with psychopathological susceptibility in both humans and animal models. We use strains of Sprague-Dawley rats inbred to show either a high locomotor response to novelty (High Responder) or a low locomotor response to novelty (Low Responder). While Low Responder (LR) rats are understood to have a higher likelihood of exhibiting depression and anxiety-like behaviors, and High Responder (HR) rats show a higher likelihood of developing addictive behavior, quantification of daily, long-term behavioral patterns has not been done to better translate them to humans. Here, we use our DHCs to quantify the long-term daily living behavior patterns in HR versus LR rats. We quantify a mixture of known stress responses and novel measures, including stress-related behaviors covering: eating, drinking, sleep, anhedonia, movement, wheel running, circadian rhythms, and over a dozen other behaviors, all with high temporal resolution. This will quantitatively detail how individuals with differing neurophenotypes (HR versus LR) experience stress to pave the way for experiments to understand and manipulate brain mechanisms for those stress responses across a variety of individuals.

Disclosures: D. Kim: None. **H. Akil:** None. **B.O. Watson:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01 NS110012
NIH T32 GM126534
Army Office of Research W911NF2410013

Title: Molecular Mechanism In The Central Amygdala But Not Parabrachial Nucleus Is Necessary For Circadian Fear Response

Authors: *K. D. DERDERIAN[1], V. ZHANG[2], H. O. DE LA IGLESIA[1];
[1]Biol., Univ. of Washington, Seattle, WA; [2]Dept. of Biochem., Howard Hughes Med. Inst., Seattle, WA

Abstract: Our laboratory has demonstrated that randomly distributed foot shocks in the foraging area of a cage, if presented during the dark phase of the light-dark cycle, can entrain rodent circadian rhythms of foraging and feeding to shift from nocturnal to diurnal. This *fear entrainment* also occurs in constant darkness (DD) without light cues when rodents are exposed to foot shocks during their active phase. Neurons in the suprachiasmatic nucleus (SCN) control circadian synchrony. Our laboratory has examined the role of the SCN by leveraging the

circadian molecular clock, which is necessary for maintaining circadian rhythms and is expressed throughout the brain. Notably, the SCN is necessary but not sufficient for fear entrainment which points to the existence of fear-entrained oscillators (FrEOs) outside of the SCN. I compared the role of several fear-associated regions, the basolateral amygdala (BLA), central amygdala (CeA), and parabrachial nucleus (PBN), as FrEOs by testing the necessity of each region for fear entrainment. Using bilateral region-specific injections of a Cre-expressing adeno-associated virus (AAV), I knocked out local *Bmal1* expression in $Bmal1^{fx/fx}$ male and female adult mice. After recovery, mice were placed in a cage with a safe nesting area connected to a foraging area for 1 week of baseline, 2 weeks of foot shocks in the foraging area during their active phase and 2 weeks of free run without shocks. CeA-targeted $Bmal1^{fx/fx}$ mice fail to entrain to foot shocks either by failing to shift their activity into the previously inactive phase or through masking behavior where mice avoid foot shocks but do not demonstrate circadian entrainment during free running conditions. This lack of entrainment is clear at both low and high shock amplitudes to which wild-type mice typically entrain. By contrast, PBN-targeted $Bmal1^{fx/fx}$ mice entrain to foot shocks. Control mice, which include wild-type mice, CeA-targeted $Bmal1^{+/fx}$ mice and $Bmal1^{fx/fx}$ mice with missed injections or injections with a non-Cre virus, also entrain to the fear stimulus. Additionally, there is no evidence of sex differences across conditions. This overall suggests that the molecular clock of the CeA plays a necessary role in fear entrainment as an FrEO whereas the PBN clock does not. However, additional research in the laboratory using optogenetic stimulation suggests that PBN stimulation is sufficient to produce fear entrainment, indicating that further research is needed to determine the mechanisms and circuitry underlying fear entrainment.

Disclosures: K.D. Derderian: None. **V. Zhang:** None. **H.O. de la Iglesia:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.16/GG13

Topic: G.07. Biological Rhythms and Sleep

Support: NIH NS131645

Title: Perineuronal net removal prevents diurnal changes in remote contextual fear conditioned memory in mice

Authors: *B. A. SORG[1], Z. ANDERSON[1], C. SEWELL[2], T. LAM[1], A. DORN[1], L. BAILEY[3], T. E. BROWN[4], K. H. OBRIETAN[5], S. D. IMPEY[6];
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Abstract: Memory retrieval requires optimal functioning for an organism's survival and varies with the time of day. Parvalbumin (PV) GABAergic neurons powerfully modify circuits needed for memory retrieval. Most PV neurons in the medial prefrontal cortex (mPFC) are enwrapped in structures called perineuronal nets (PNNs), which restrict plasticity in adulthood and are vital for precise firing of PV neurons. We previously reported that the expression of PNNs and PV exhibit a diurnal pattern in the rat mPFC, and propose that this diurnal pattern is a major factor driving diurnal differences in memory retrieval. Mice were trained at ZT10 and tested 3 wks later for contextual fear at either ZT4 or ZT16, the peak and nadir, respectively, for fear retrieval that we pilot tested. 24 h later, they were tested at ZT4 or ZT16 in an auditory fear extinction session in a different chamber, and then at these same ZT times in a test for auditory fear extinction memory 24 h later. Female mice showed a near-significant level of higher freezing during extinction of auditory fear at ZT4 vs ZT16 and also higher freezing at ZT4 on the test for extinction memory. Males demonstrated higher contextual conditioning at ZT4 than at ZT16. They also showed higher auditory fear at ZT4 during both the fear extinction session and the extinction memory test, similar to that of females but more pronounced. We used slice electrophysiology to assess inhibitory tone onto mPFC pyramidal neurons. In both males and females, there was an increase in inhibitory events at ZT16 compared to ZT4. However, only males had increased PV interneuron excitability at ZT16, suggesting that there may be a sex effect underlying changes in inhibitory tone. We next tested the impact of removing PNNs in the mPFC using chondroitinase ABC (ABC). Male mice were trained at ZT10 and 2 weeks later given surgery for intra-mPFC penicillinase control or ABC, and then tested for remote contextual and auditory fear conditioning 1 week later at ZT4 or ZT16. At ZT4, ABC reduced contextual fear conditioning but did not alter auditory fear during the extinction session or the extinction memory test, suggesting an impact of mPFC PNN removal on hippocampal-mPFC communication. At ZT16, experiments thus far showed a trend toward increasing contextual fear after ABC treatment. Further experiments are ongoing to assess electrophysiological changes following PNN removal at both timepoints. Overall, PNN removal in the mPFC appears to flatten the diurnal rhythms of remote fear memory retrieval. These findings suggest that PNNs contribute to diurnal rhythms in the retrieval of remote contextual fear memory.

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Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.17/GG14

Topic: G.07. Biological Rhythms and Sleep

Support: NIH NS133381
NS131728

Title: Hippocampal interneurons under GABAergic control during sharp wave-ripples

Authors: *G. G. SZABO[1], B. VARGA[1], J. S. FARRELL[2,3], B. DUDOK[1,4], T. GSCHWIND[1], C. VARGA[5], I. SOLTESZ[1];
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Abstract: Short, high-frequency electrographic events, called sharp wave-ripples (SPW-Rs) can be recorded during the resting states of the brain and are critically involved in learning and memory. In the hippocampus, where SPW-Rs are generated, distinct types of interneurons show diverse activity dynamics during these oscillations. The recently described TORO (theta-OFF/ripple-ON) cells are GABAergic neurons that show particularly robust spiking activity during SPW-Rs but reduced firing during theta activity. We previously showed that TORO cells preferentially target other GABAergic neurons, predicting the occurrance of interneurons with activity patterns opposite to TOROs. To test the latter hypothesis, we used high-throughput two-photon imaging to monitor the activity of GABAergic interneurons throughout the dorsal CA1 region of the hippocampus while detecting SPW-Rs. We found that interneurons displaying reduced activity during SPW-Rs and increased activation during running-associated theta periods can indeed be observed across all layers from stratum oriens to stratum lacunosum-moleculare. To further characterize cells with such behaviors, we combined immunhistochemical techniques with two-photon imaging and juxtacellular recordings in awake mice. These experiments revealed that select subsets of GABAergic cells that show suppressed activity during SPW-Rs can be found both in the cannabinoid receptor type-1 (CB1R) -expressing, and the parvalbumin (PV) -expressing subclasses. In addition, these subsets of cells receive strong inhibition from neurons that express the muscarinic type 2 receptor, a molecular marker that is a characteristic feature of TORO cells. Our findings outline a hippocampal disinhibitory network composed of specific subsets of dendrite- and perisomatic region-targeting interneurons regulated by TORO cells that represents a critical circuit element in SPW-R mediated learning and memory mechanisms. Funded by the NIH NS133381 and NS131728 (to I.S.).

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Poster

PSTR068: Biological Clocks and Rhythms

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Program #/Poster #: PSTR068.18/GG15

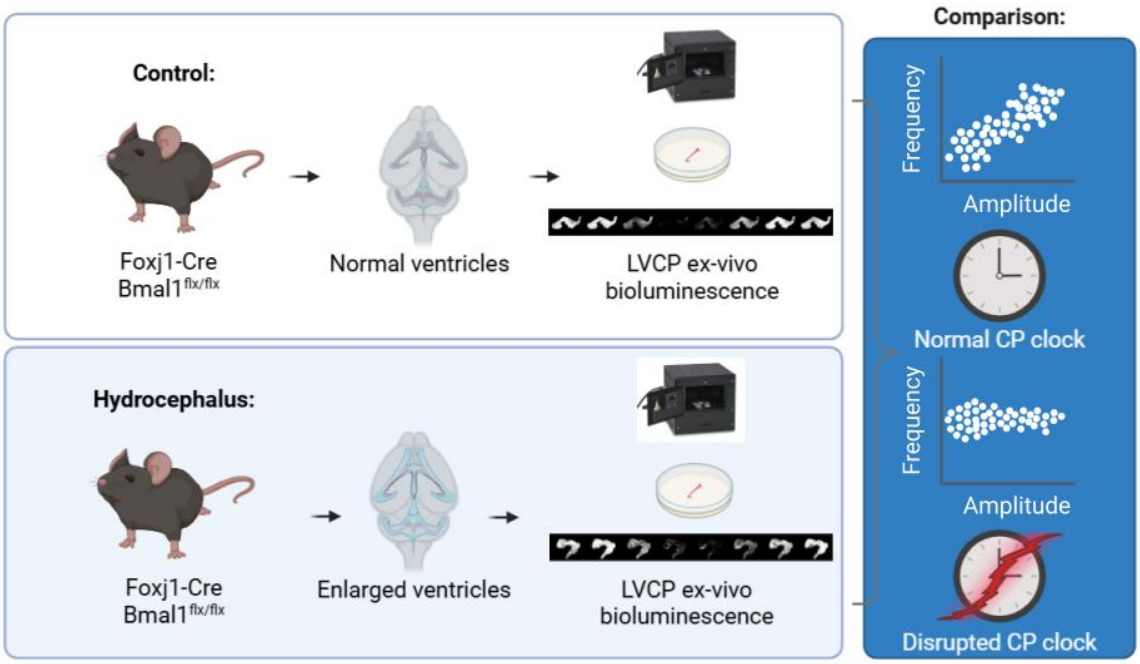
Topic: G.07. Biological Rhythms and Sleep

Support: National Science and Technology Council (NSTC) 114-2320-B-038-052-MY3
Fulbright U.S. Student Program, Fulbright Taiwan, Foundation for Scholarly Exchange

Title: Timing is everything: investigating choroid plexus circadian dysfunction in hydrocephalus

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Abstract: Circadian rhythm disruption is a common phenomenon in neurological conditions and may accelerate disease progression. While the suprachiasmatic nucleus (SCN) is the master circadian clock, there has been increased interest in the circadian role of the choroid plexus (CP), a peripheral circadian oscillator that produces cerebrospinal fluid (CSF), given that CSF production and waste clearance are circadian. Previous studies have implicated CP dysfunction in fluid homeostasis impairment and hydrocephalus, which are characterized by impaired waste clearance and altered CSF dynamics, respectively. However, how changes in the SCN-CP phase relationships and CP oscillator coupling may lead to disrupted CP circadian organization and altered CSF dynamics is still largely unexplored. To study CP circadian organization and altered CSF dynamics, ex vivo bioluminescence recordings from spontaneous and tamoxifen-induced FoxJ1-Cre recombination hydrocephalus models were used to quantify period, amplitude, and synchrony between CP cell clusters. In the hydrocephalus samples, while non-hydrocephalus control mice showed a negative correlation between period and amplitude, a subset of hydrocephalus mice had no correlation, potentially indicating disruption of oscillator coupling dynamics (twist), a mechanism linking period and amplitude regulation in circadian networks (Myung et al., 2018). Together, these findings suggest that CP circadian organization is altered in neurological disorders affecting distinct aspects of CSF homeostasis. The convergence of altered circadian rhythms and disrupted CP oscillator coupling in hydrocephalus identifies CP circadian dysfunction as a potential mechanism underlying neurological disease.



Disclosures: L.I.J. Byer: None. **V.H. Truong:** None. **J. Myung:** None.

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

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Program #/Poster #: PSTR068.19/GG16

Topic: G.07. Biological Rhythms and Sleep

Support: Keck Foundation
R01 DK119811
R01 AG082349

Title: Temporal organization of neuroimmune gene transcripts across the brain are affected by acute jet-lag

Authors: *P. REIS[1], G. DENAROSO[4], N. SANTOS[5], B. BACA[6], J. WANG[7], G. PEARSON[2], S. AKLI[3], I. N. KARATSOREOS[8];
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Abstract: An organism's internal rhythms align to the external environment via molecular clocks, which operate in almost every mammalian cell. Across the brain, molecular clocks drive transcriptional rhythms to organize region-specific functions across a day. Neuroimmune processes are critically important in the regulation of inflammatory processes and tissue homeostasis, and when perturbed may contribute to initiation or exacerbation of neurodegeneration. Yet little is known about how these rhythms differ across regions, and how light cycle perturbations impact transcriptional rhythms that alter cellular activities. To address this question, we measured the expression of neuroimmune transcripts from two brain regions across a day, after housing mice in a standard light-dark cycle or after a single 6h "jet-lag" paradigm. To accomplish this, we housed mice in a standard 12:12 light:dark schedule and then exposed one-half to a jetlag model (single 6h phase advance). We then collected male and female mice 24h after the new lights on, at 8 times of day, every 3h (n=3/time point). Brains were flash frozen and 0.5mm x 1mm punches were collected from the somatosensory cortex and dorsal hippocampus, two regions associated with learning, memory and mood, and demonstrated to be sensitive to environmental stressors. RNA was extracted from each sample and was run on a Nanostring's nCounter Neuroinflammation panel, which probed for up to 750 neuroimmune transcripts. To compare rhythms across brain region, sex, and lighting condition, we used Nanostring's nSolver software and DiffCircaPipeline, an analysis package for detecting rhythms in gene transcripts. We found the temporal pattern and number of rhythmic neuroimmune transcripts differed across brain regions, with each region expressing unique combinations of rhythmic transcripts. We also found differences in phase of shared rhythmic transcripts across brain regions. These changes indicate many neuroimmune-related transcripts are rhythmic even

under standard (i.e., homeostatic) conditions, and the presence and timing of these rhythms exhibit specificity across brain regions. Furthermore, jet lag alters the pattern of gene expression in brain regions, impacting pathways such as microglial function, matrix remodeling, and oligodendrocyte function. This suggests neuroimmune pathways are differentially regulated across brain regions, and that they become dysregulated under a light shift in a region-specific manner.

Disclosures: P. Reis: None. **G. Denaroso:** None. **N. Santos:** None. **B. Baca:** None. **J. Wang:** None. **G. Pearson:** None. **S. Akli:** None. **I.N. Karatsoreos:** None.

Poster

PSTR068: Biological Clocks and Rhythms

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Program #/Poster #: PSTR068.20/GG17

Topic: G.07. Biological Rhythms and Sleep

Support: Querrey-Simpson Institute for Bioelectronics
NIMH grant R44MH140096

Title: Continuous dual-site wireless temperature monitoring reveals circadian and metabolic dynamics in freely moving mice

Authors: *C. H. GOOD[1,2], D. HINTERMUELLER[1,2], I. JONES[1,2], C. SHAW[1,2];
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Abstract: Body temperature is a sensitive indicator of circadian state, metabolic activity, and systemic health, yet existing telemetry systems are limited by battery life (e.g. recording duration), sampling rate, and implant size. To overcome these limitations, we developed a miniaturized implantable, wirelessly rechargeable (13.56 MHz; NFC), temperature monitoring platform (nTemp) capable of uninterrupted sensing with accuracy within 0.08°C in freely moving animals. The platform supports adjustable sampling rates tailored to experimental needs, allowing lower-frequency acquisition (e.g. 1 sample/minute) for circadian studies and higher frequency sampling (e.g. 1 sample/second) for rapid onset thermoregulatory, metabolic, and drug-response investigations. Repeated wireless recharging every 3-4 weeks enables longitudinal recordings extending beyond four months and supports studies spanning much of the animal's lifespan. To validate the device, 12 mice were continuously monitored under a 12-h light/12-h dark cycle in a vivarium using nTemp sensors configured to simultaneously acquire core and subdermal (skin) temperature measurements. Continuous recordings revealed robust circadian temperature oscillations, with elevated temperatures during the dark (active) phase and a dominant periodicity of approximately 24 h. High-resolution measurements additionally suggested the presence of recurring ultradian thermal events embedded within the circadian cycle. These events were associated with transient increases in physical activity and were

consistently observed across recording periods. Simultaneous core and skin temperature measurements further resolved dynamic thermoregulatory relationships across behavioral state transitions and environmental conditions by capturing temporal changes in body temperature gradients. These findings demonstrate the utility of our dual-sensor temperature device as a scalable platform for long-term physiological monitoring. We establish body temperature as a high-resolution reference signal for studies of circadian biology, metabolism, gastrointestinal physiology, and therapeutic development.

Disclosures: C.H. Good: A. Employment/Salary (full or part-time):; NeuroLux, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroLux, Inc. **D. Hintermueller:** A. Employment/Salary (full or part-time):; NeuroLux, Inc. **I. Jones:** A. Employment/Salary (full or part-time):; NeuroLux, Inc. **C. Shaw:** A. Employment/Salary (full or part-time):; NeuroLux, Inc..

Poster

PSTR068: Biological Clocks and Rhythms

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR068.21/GG18

Topic: G.07. Biological Rhythms and Sleep

Support: R01 DK119811
R01 AG082349

Title: Perinatal environmental circadian disruption affects prefrontal cortex development through early life in male and female mice

Authors: *J. WANG[1], M. J. HARTSOCK[2], G. PEARSON[3], I. N. KARATSOREOS[4]; [1]Univ. of Massachusetts, Amherst Neurosci. and Behavior Program, Amherst, MA; [2]Psychology and Neurosci., Univ. of Colorado Boulder Dept. of Psychology and Neurosci., Amherst, MA; [3]Neurosci. and Behavior, Univ. of Massachusetts Amherst, Amherst, MA; [4]Psychological and Brain Sci., Univ. of Massachusetts, Amherst, MA

Abstract: The prefrontal cortex (PFC) regulates cognitive and emotional behaviors. Notably, disruption of the circadian clock impairs cognitive ability and increases risk for depression and anxiety. In mice, environmental disruption of circadian rhythms alters PFC neuronal morphology. Moreover, growing evidence shows that circadian rhythms are important for synaptic formation and maintenance, which can impact circuit integrity and structure. Early development is a critical period for synaptic growth and maturation and is sensitive to environmental disruptions. Our published work shows that perinatal circadian disruption (pECD; housing in a 20h light-dark cycle; T20) during gestation through weaning produces lasting, sexually dimorphic effects in offspring despite their being returned to normal T24 conditions. In males, pECD reduced body weight into adulthood, fragmented sleep during the dark (active)

period, increased light-period sleep, altered postsynaptic dynamics of excitatory release onto PFC pyramidal neurons, and blunted time-of-day differences in intrinsic cell properties. Females were largely protected behaviorally, but still showed synaptic changes, including loss of the diurnal pattern in postsynaptic EPSC components. To identify mechanisms that are affected by circadian disruption during early life, we asked if pECD influences gene expression within the frontal cortex (FC)/PFC. To test this, we subjected pregnant C57BL6N dams to either control T24 or disrupted T20 light cycles which were maintained through the weaning period. Pups were weighed just after birth at postnatal day (P)0, and then again at P21. FC of P0 pups and PFC of P21 pups were collected, RNA extracted and run on a Nanostring nCounter mRNA expression panel. Interestingly, pECD had significant effects on genes that participate in pathways modulating synaptic plasticity, dendritic spine stabilization, and excitatory-inhibitory balance within FC/PFC that remains consistent, and these effects were maintained through to P21. These effects were sex dependent, further extending our initial findings. The impact of these changes will be explored through a variety of future experiments, including effects on fear learning and recall, as well as morphological changes suggesting that disruptions in early life can compromise PFC development and function into adulthood. Together, our data shows that pECD heavily influences the trajectory of neural development within the FC/PFC during early development as measured by transcriptional changes, in a sex dependent manner, which is associated with behavioral and electrophysiological changes observed into adulthood.

Disclosures: J. Wang: None. **M.J. Hartsock:** None. **G. Pearson:** None. **I.N. Karatsoreos:** None.

Poster

PSTR068: Biological Clocks and Rhythms

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Topic: G.07. Biological Rhythms and Sleep

Support: National Science and Technology Council (NSTC) 114-2320-B-038-052-MY3

Title: Intrinsic Circadian Heart Rate Regulation in the Embryonic Heart Before Mature SCN-Dependent Autonomic Innervation

Authors: V. H. TRUONG, H. VITET, ***L. PALANIVELU**, J. MYUNG;
Grad. Inst. of Mind, Brain, and Consciousness (GIMBC), Taipei Med. Univ., New Taipei, Taiwan

Abstract: In adult mammals, circadian heart rate (HR) rhythms are generally attributed to regulation by the suprachiasmatic nucleus (SCN) through autonomic and neurohumoral pathways. At the same time, local cardiac clocks regulate ion channel expression and cardiac electrophysiology, indicating an intrinsic capacity for circadian control within the heart. The extent to which rhythmic HR depends on central signals versus local cardiac circadian clock

remains unresolved. In adults, central and peripheral clocks are already established and tightly coupled, making it difficult to distinguish the relative contribution of SCN-dependent signals and intrinsic cardiac circadian regulation *in vivo*. The embryonic heart provides a developmental model to address this question. We therefore examined the relationship between molecular clock activity and HR rhythms in embryonic mouse hearts before the establishment of functional SCN innervation. Using PER2::LUC bioluminescence reporter recordings combined with high-frame-rate, time-differential brightfield imaging, we simultaneously monitored molecular clock activity and spontaneous beating rhythms in embryonic heart explants. Early in development, PER2::LUC signal showed circadian rhythmicity first, followed by circadian HR. The lag between molecular and HR rhythms gradually increased and stabilized by E16.5, with HR rhythms consistently lagging behind PER2::LUC oscillations. *In vivo* qPCR analysis revealed developmental upregulation of core clock genes, including *Rev-Erbα, Rev-Erbβ, Bmal1, Dbp, Cry2, and Rorα,* with expression levels increasing from mid-gestation onwards. In parallel, several ion channel and excitability-related genes, notably, *Cacna1g*, *Kcnd2 and Scn5a* showed early rhythmic expression patterns that coincided with clock gene activation. In contrast, pacemaker-associated genes, *Hcn1* and *Hcn4*, became more prominent at later embryonic stages. These transcriptional changes suggest coordinated maturation of molecular clock and electrophysiological pathways that support rhythmic cardiac function. Together, our findings demonstrate that circadian HR regulation can arise locally within the embryonic heart prior to the maturation of SCN-dependent autonomic innervation. The coordinated maturation of clock and excitability-associated ion channel genes supports the emergence of an intrinsic cardiac circadian system capable of coupling molecular clock activity to physiological output during embryonic development.

Disclosures: V.H. Truong: None. **H. vitet:** None. **L. Palanivelu:** None. **J. Myung:** None.

Poster

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Topic: G.07. Biological Rhythms and Sleep

Support: National Science and Technology Council (NSTC) 114-2320-B-038-052-MY3

Title: Dorsal-ventral dissociation of suprachiasmatic nucleus oscillators reveals a potential mechanism for emergent multidien rhythms

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Abstract: The mammalian suprachiasmatic nucleus (SCN) is organized into dorsal (D-SCN) and ventral (V-SCN) oscillator populations that are normally coupled to generate coherent circadian rhythmicity. However, partial dissociation between SCN subregions can occur under some physiological and experimental conditions. Here, we investigated whether interactions between D-SCN and V-SCN oscillators can generate temporal dynamics beyond the circadian range. Locomotor activity recordings in constant darkness revealed spontaneous multidien (multi-day infradian) fluctuations in a subset of mice, with preliminary results suggesting an association with age. We hypothesized that these long-period rhythms arise from beating between partially desynchronized SCN oscillators that differ slightly in period and phase. To test this hypothesis, we used a 7:5:7:5 LDLD light schedule to induce behavioural bifurcation to induce dorsal-ventral dissociation. Bioluminescent PER2::LUC and Bmal1-ELuc reporter recordings revealed robust dissociation between D-SCN and V-SCN oscillators, including near-antiphasic relationships. Notably, V-SCN became more phase-advanced than D-SCN, reversing the D-SCN-leading phase relationship typically observed under standard 12:12 LD conditions. We then developed a mathematical model of D-V oscillators with weak negative coupling. The model reproduced the observed phase relationships and predicted that weak coupling, together with small differences in intrinsic period, can generate slow beating dynamics, with a power spectrum showing peaks at 10-20 days, comparable to those observed in locomotor activity. These findings suggest that multidien behavioral rhythms can emerge from intrinsic interactions between intrinsically independent SCN subregions. Importantly, such dynamics may be difficult to detect under typical physiological conditions and may require very long duration sampling windows. LDLD-induced bifurcation therefore provides an experimental framework for revealing latent dorsal-ventral SCN dynamics by amplifying phase separation between oscillator subpopulations.

Disclosures: V.H. Truong: None. **P. Chang:** None. **H. Piggins:** None. **J. Myung:** None.

Poster

PSTR068: Biological Clocks and Rhythms

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Program #/Poster #: PSTR068.24/GG21

Topic: G.07. Biological Rhythms and Sleep

Support: National Science and Technology Innovation 2030 Major Program 2021ZD0202205
National Science and Technology Innovation 2030 Major Program 2022ZD0211903
Beijing Municipal Science and Technology Commission Z251100000725008

Title: Multiscale time computation through coordinated fast and slow Ca^{2+} dynamics in the suprachiasmatic nucleus

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Abstract: The suprachiasmatic nucleus (SCN) is the mammalian central clock, with each neuron harboring a molecular clock known as transcription-translation feedback loop (TTFL). Recent in vitro studies have shown that SCN population Ca^{2+} dynamics support system-level time computation. However, how SCN population dynamics support multiscale time computation *in vivo* and how TTFL interacts with these dynamics remain enigmatic. Here, we investigated in vivo time computation and its integration with behavioral states. Using improved miniature two-photon microscopy, we continuously recorded GABAergic neuronal Ca^{2+} dynamics in freely behaving mice for 48 hours. Machine learning revealed that multiscale timekeeping is supported by coordinated fast and slow Ca^{2+} dynamics, with fast components enabling fine-scale resolution. Interestingly, Ca^{2+} dynamics predicted sleep-wake states and responded to light-dark transitions. Deletion of the TTFL core gene *Bmal1* diminished neuronal rhythmicity and destabilized fast Ca^{2+} dynamics, impairing fine-scale time computation and responses to sleep-wake and light-dark transitions. These findings indicate that multiscale SCN time computation relies on coordinated fast and slow Ca^{2+} dynamics integrated with behavioral states and environmental cues.

Disclosures: J. Yu: None. **X. Fang:** None. **H. Cheng:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.01/GG22

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Korea NRF Grant RS-2025-02653047 (JB)
Marie Sklodowska-Curie Global Fellowship - AstroError (MC)
NIH Grant R01MH126351 (MS)
NIH Grant R01MH133066 (MS)
NIH Grant R01NS130361 (MS)

Title: Learning-dependent coordination and functional dissociation of norepinephrine and dopamine signaling in mouse anterior cingulate cortex

Authors: *J. BAE, Z. WANG, M. CELOTTO, R. M. LAM, T. OSAKI, M. SUR;
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Abstract: Norepinephrine (NE) and dopamine (DA) systems are both implicated in multiple components of learned behavior. However, it remains unclear how these two neuromodulatory systems are coordinated within the same behavioral context and whether similar activity dynamics reflect shared or distinct functional roles. We focused on the mouse anterior cingulate cortex (ACC), a region implicated in contextual and executive functions, that receives both locus

coeruleus (LC)-NE and ventral tegmental area (VTA)-DA projections. To directly compare NE and DA dynamics, we measured signals from genetically encoded fluorescent sensors simultaneously during classical conditioning and instrumental learning tasks, combined with DREADD-mediated inhibition of LC or VTA neurons. In a separate cohort, we performed two-photon imaging of axon terminals arising from LC and VTA to compare terminal-level dynamics. We first found that NE and DA signals showed similar phasic responses to random salient events, including water delivery and air puff. During classical conditioning, both NE and DA responses shifted toward the cue as mice learned the task, consistent with temporal-difference learning. Moreover, the single-trial correlation between NE and DA signals increased when the reward cue was presented in the well-trained stage, suggesting that the interaction between these systems is context- and learning-dependent. In an instrumental learning task with variable stimulus evidence, both NE and DA signals during the cue period were positively correlated with tone intensity, indicating that both systems encode graded reward expectation. However, DREADD-mediated inhibition of LC and VTA revealed a functional dissociation between the two systems: LC inhibition decreased the false alarm rate, whereas VTA inhibition increased it. Together, these findings suggest that NE and DA signals are coordinated during learned behavior but exert distinct causal effects on specific components of behavioral control.

Disclosures: J. Bae: None. **Z. Wang:** None. **M. Celotto:** None. **R.M. lam:** None. **T. Osaki:** None. **M. Sur:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.02/GG23

Topic: H.02. Reward and Appetitive Learning and Memory

Support: ZIA-DA000434
K99-DA062788

Title: Characterization of nucleus accumbens dopamine during operant positive and negative reinforcement

Authors: *J. J. CHOW[1], E. PILZ[3], K. M. COSTA[4], G. SCHOENBAUM[2], Y. SHAHAM[5]; [1]NIDA IRP, Baltimore, MD; [2]NIDA IRP, BALTIMORE, MD; [3]NIDA, Baltimore, MD; [4]Psychology, UAB, Birmingham, AL; [5]Behavioral Neurosci. Br., IRP/NIDA/NIH, Baltimore, MD

Abstract: Background: We previously reported that operant social self-administration in rats is associated with phasic dopamine activity in the nucleus accumbens (NAc) core after lever insertion and a gradual increase just prior to lever press (Chow et al. J Neurosci 2024). Here, we used within-subject procedure to measure dopamine and serotonin in NAc core during social and food self-administration (positive reinforcement) and operant shock escape/avoidance (negative

reinforcement).
Methods: We trained rats (n = 12; 6 females) to lever-press for food (45-mg pellet/trial) and social interaction (15-s access to same-sex peer/trial) on a fixed ratio-1 reinforcement schedule, 45 min sessions/reward. We then trained rats to lever-press to escape and then avoid mild-shock footshocks (0.14-0.28 mA). Next, we transfected GRAB-DA2m and GRAB-r5HT1.0 and implanted optic fibers into NAc core. We then measured dopamine and serotonin during food, social, and shock escape/avoidance sessions.
Results: Rats reliably acquired the tasks. Dopamine results for social reward replicated our published results, showing phasic increases after lever insertion (>0.5-s) and gradual increases (~2-s) just prior to lever press. Food reward produced a similar pattern, but responses after lever insertion and before lever press were ~2-3 fold larger. In contrast, during shock escape/avoidance, phasic dopamine decreases were observed following the warning tone, lever insertion, and shock delivery. In contrast, both escape and avoidance responses were preceded by a gradual increase (~1-s) in dopamine just before lever press. We are currently analyzing the serotonin data and will present these results at the conference.
Conclusions: Results suggest that NAc core dopamine signaling reflects the valence of both positive and negative reinforcers.

Disclosures: J.J. Chow: None. **E. Pilz:** None. **K.M. Costa:** None. **G. Schoenbaum:** None. **Y. Shaham:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.03/GG24

Topic: H.02. Reward and Appetitive Learning and Memory

Support: 1K01DA060994-01

Title: Dopaminergic Modulation of Hippocampal Memory via Astrocyte-Neuron Circuit Mechanisms

Authors: *L. J. CODISPOTI[1], S. KRISHNAN[2];
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Abstract: Acquisition and retention of learned behaviors depend on memory consolidation, a process in which newly acquired information is progressively stabilized and reorganized across hippocampal and neocortical networks. During systems consolidation, the hippocampal CA1 subregion is central to encoding episodic and spatial information, making it a principal locus for investigating molecular and circuit mechanisms that influence post-learning network reorganization. While neuronal mechanisms supporting hippocampal-dependent learning have been extensively studied, the involvement of non-neuronal cells in post-learning circuit plasticity remains unclear. Astrocytes are morphologically complex glial cells that actively regulate

synaptic transmission, neuronal excitability, and extracellular homeostasis. Within this framework, astrocytic ensembles respond to and influence neurotransmitter signaling and plasticity, positioning them as critical regulators of learning and memory. However, their role in hippocampal circuit dynamics with respect to astrocyte–neuron interactions during reward-associated memory formation remains unresolved. Prior work in the lab has implicated dopamine in stabilizing hippocampal memory formation, and both astrocytes and neurons express dopamine receptors; yet the cellular mechanisms by which dopamine may influence astrocyte–neuron coupling and memory are unclear. We hypothesize that dopaminergic modulation during memory formation influences astrocyte–neuron coupling in CA1, driving cellular and subcellular changes that shape behavioral expression of learned information. Consistent with this hypothesis, pharmacological manipulation of dopaminergic signaling (D1R agonism and PLCβ inhibition) altered object location memory performance, indicating dopaminergic regulation of hippocampal-dependent spatial memory. To investigate dopaminergic modulation of astrocyte–neuronal coupling, we used simultaneous in vivo two-photon calcium imaging of hippocampal CA1 neurons expressing CAMKII-jRCaMP and astrocytes expressing GFAP-GCaMP. We used a head-fixed paradigm where mice navigate familiar and novel virtual environments and receive water rewards via a lick spout to assess reward-guided learning, and pharmacologically manipulated dopamine to capture its role in modulating astrocyte–neuron activity in vivo. This approach enables concurrent measurement of behavioral and cellular activity, allowing direct linkage of the astrocyte–neuron interface to behavior and providing a framework for understanding how dopaminergic modulation shapes memory-related circuit function.

Disclosures: L.J. Codispoti: None. **S. Krishnan:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

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Program #/Poster #: PSTR069.04/HH1

Topic: H.02. Reward and Appetitive Learning and Memory

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NIH F31DA060046

Title: Amygdala dopamine function in model-based reward learning.

Authors: *A. K. CRAWLEY[1], A. SHAMOONY[1], B. MUNOZ[1], K. WILSON[1], K. I. RAMIREZ-ARMENTA[1], J. GIOVANNIELLO[3], K. M. WASSUM[2];

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Abstract: When making decisions, we can use an encoded internal model of our actions and their consequences to prospectively evaluate our choices and select those that led to the most advantageous outcomes. Such encoded action-outcome associations support goal-directed decision making. The basolateral amygdala (BLA) is involved goal-directed behavior and may be supported in this function by dopamine. Midbrain dopamine neurons increase firing in response to unexpected reward and this is thought to serve as a teaching signal to support multiple forms of learning. Here we explored the function of BLA dopamine in the action-outcome learning underlying goal-directed decision making using fiber photometry dopamine sensor imaging, cell-type- and pathway-specific optogenetic inhibition, instrumental conditioning, and outcome-specific devaluation tests of goal-directed decision making. We compared this to the function of BLA dopamine in the Pavlovian cue-reward learning that can also support predictions for adaptive behavior. During both instrumental and Pavlovian conditioning, earned rewards trigger dopamine release in the BLA. Whereas this reward-evoked dopamine is critical for cue-reward learning, it is dispensable for action-outcome learning. Preliminary results suggest, however, reward-evoked BLA dopamine may mediate the ability to form hierarchical cue-action-outcome associations. These findings suggest that BLA dopamine contributes differently in associative learning, being necessary for cue-reward learning but not for action-outcome associations, while contributing to the formation of hierarchical cue-action-outcome associations that support adaptive decision making. Overall, this work advances our understanding of the neural mechanisms underlying adaptive decision making by identifying how dopamine signaling in the basolateral amygdala differentially supports the formation of reward-related associations.

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Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01DA055018

Title: The role of nucleus accumbens cholinergic interneuron D5 dopamine receptors in motivated behavior

Authors: *N. ISMAYILZADA[1], N. KAPUSTA[2], G. JAMMAR[2], E. F. GALLO[2]; [1]Fordham University, Grad. Sch. of Arts and Sci., Bronx, NY; [2]Biol. Sci., Fordham Univ., Bronx, NY

Abstract: Nucleus accumbens (NAc) dopamine is critical for diverse aspects of motivated behavior. While dopamine D1 and D2 receptor modulation of striatal neurons has been extensively documented, much less is known about the behavioral roles of D5 receptors (D5Rs). In NAc, D5Rs are found in cholinergic interneurons (CINs), which powerfully influence dopamine release and striatal plasticity. Thus, NAc D5Rs are prime candidates for shaping motivated behavior, yet functional studies have remained limited by a lack of selective targeting approaches. Here, we developed NAc-selective D5R knockdown mice (NAc-D5KD) using AAV-Cre injections into the NAc core of adult Drd5-flox mice. RNAscope in-situ hybridization analysis revealed that NAc D5R expression was restricted to CINs. We confirmed a 55% reduction in D5R levels in CINs expressing Cre vs mCherry. We then investigated the effect of D5R knockdown on distinct motivated behavior domains that critically depend on NAc dopamine signaling. To evaluate the role of CIN D5Rs in impulsive decision-making, male and female NAc-D5KD and mCherry-expressing mice were first tested on a delay discounting task. Both groups discounted large, delayed rewards, and while NAc-D5KD mice showed a trend toward reduced impulsive choice, this was not statistically significant (virus x delay: $p = 0.089$, N=26). Moreover, NAc-D5KD mice showed normal inhibitory responding in a Go/No-Go task. These results suggest that CIN D5Rs are not required for impulsive choice or actions. Next, we sought to determine whether CIN D5Rs mediate behavioral adaptations and rewarding properties associated with cocaine. Neither cocaine sensitization (15 mg/kg) nor place preference were altered by D5R downregulation. Finally, to determine whether CIN D5Rs contribute to motivation for a food reward, a separate cohort was tested using a progressive ratio (PR) task with an exponential increase in lever pressing demand. Compared to controls, NAc-D5KD mice showed a significantly increased responding in the first PR session (lever presses: NAc-D5KD = 1702 ± 131, Ctrl = 1041 ± 155, $p = 0.007$, N=15). This effect, however, was not observed in the next two sessions, indicating that D5R downregulation results in increased willingness to expend effort when steep lever-pressing demands are first introduced. Together, our findings suggest that CIN D5Rs in NAc contribute to adaptive disengagement from reward-seeking following unexpected effort escalation. These results highlight the distinct contribution of NAc D5 dopamine receptors to the dopaminergic modulation of reward-related behaviors.

Disclosures: N. Ismayilzada: None. **N. Kapusta:** None. **G. Jammar:** None. **E.F. Gallo:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Institute on Drug Abuse (R01 DA045783)
National Institute of Mental Health (R01 MH129582)
State of California

Title: Anterior and posterior dopamine domains in the accumbens core

Authors: *S. KANG, D. A. BURKE, F. FAROUQ, C. KORNBREK, H. JEONG, V. K. NAMBOODIRI, J. D. BERKE;
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Abstract: Dopamine (DA) signaling in the nucleus accumbens (NAc) core is implicated in motivation, mood, and reward-guided learning, yet how DA activity within the core supports these functions remains unresolved. Many models treat core DA as a unified signal, but this idea has been difficult to test because conventional DA measurements provide limited spatial coverage. We used two-photon imaging of the DA sensor dLight3.8 through chronically implanted microprisms in awake, head-fixed mice (n = 5) to monitor DA dynamics across a ~1.5 × 1.5 mm field of view spanning much of the anterior-posterior extent of the NAc core at >205 Hz. Core DA dynamics separated into distinct anterior and posterior domains. Anterior core showed higher tonic DA-related signals than posterior core, even though spontaneous transients were less frequent anteriorly under baseline conditions. Cocaine further elevated tonic DA-related signals, most prominently in anterior core. Anterior phasic responses were valence-sensitive, increasing to sucrose rewards and decreasing to aversive heat. In contrast, posterior core showed larger phasic increases to unexpected sucrose rewards, more frequent spontaneous transients under baseline conditions, and positive responses to both rewarding and aversive stimuli. During Pavlovian conditioning, cue-evoked DA responses emerged with a posterior bias, whereas reward responses became more spatially distributed after learning. These findings show that DA signaling in the NAc core is not spatially uniform, but consists of separable anterior and posterior dynamics. This organization argues against unitary models of core DA function and highlights the value of high-resolution deep-brain DA imaging for revealing spatial structure that can be obscured by averaged measurements.

Disclosures: S. Kang: None. **D.A. Burke:** None. **F. Farouq:** None. **C. Kornbrek:** None. **H. Jeong:** None. **V.K. Namboodiri:** None. **J.D. Berke:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

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Program #/Poster #: PSTR069.07/HH4

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R01MH137461

Title: Dopamine Modulation and D1R/D2R mPFC Neuronal Dynamics During Approach-Avoidance Conflict

Authors: *B. P. KEARNEY, L. A. DENARDO;
Physiol., UCLA, Los Angeles, CA

Abstract: The medial prefrontal cortex (mPFC) plays a critical role in adaptive behavior, particularly when animals must balance reward approach with threat avoidance. Dysregulation of

mPFC circuit activity, including dopamine (DA) signaling, is implicated in psychiatric disorders marked by maladaptive avoidance, including anxiety, post-traumatic stress disorder, depression, and substance use disorder. The mPFC receives DA input from the ventral tegmental area and plays a central role in integrating real time appetitive and aversive contextual information with previously learned strategies to guide flexible action selection. However, how DA dynamically modulates distinct mPFC neuronal populations during approach-avoidance conflict remains poorly understood. Here, we use the platform-mediated avoidance assay to investigate DA signaling and dopamine D1 receptor (D1R) or dopamine D2 receptor (D2R) expressing neuronal activity within the mPFC during platform mediated avoidance (PMA). In this task, mice learn to avoid a tone-signaled foot shock by stepping onto a safety platform, at the cost of temporarily forfeiting access to a sweet reward. To simultaneously monitor dopaminergic and cell-type-specific activity, we performed dual-color fiber photometry in the mPFC using GRAB-DA3h to record DA release and Cre-dependent sRGECO to record calcium activity from D1R+ or D2R+ neurons in corresponding Cre driver lines across threat learning and retrieval. Experiments in D1-Cre mice revealed dynamic, task-locked changes in both mPFC DA release and D1R+ calcium activity during discrete task epochs, including threat-predictive cues, aversive outcomes, and approach-avoidance behaviors. These responses evolved across training as animals learned to preemptively avoid danger, suggesting that DA and D1R+ neuronal activity are recruited in a learning and context dependent manner. We also observed distinct activity patterns surrounding entries and exits of the safe location, indicating that mPFC DA and D1R+ neurons may differentially encode behavioral transitions between avoidance and reward-seeking states. Ongoing experiments extend this dual-color photometry approach to D2R+ mPFC neurons and suggest that D1R+ and D2R+ populations may exhibit distinct DA modulation and behavioral encoding features during PMA. Overall, these studies help define how mPFC DA signaling and D1R+/D2R+ neuronal dynamics are coordinated during approach-avoidance conflict.

Disclosures: B.P. Kearney: None. **L.A. DeNardo:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

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Program #/Poster #: PSTR069.08/HH5

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Dopamine signaling in nucleus accumbens underlies reward devaluation by repeated consumption

Authors: *Y. LEE, Y.-B. KIM, H. CHOI;
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Abstract: Depending on the environment, context, and task at hand, the novelty or familiarity of a stimulus can be either appetitive or aversive. While individuals often prefer familiar foods, excessive access to the same option can lead to negative motivational value, driving a search for

alternative food sources. This could be explained by “Sensory-specific Satiety (SSS)” - a key mechanism of reward devaluation - wherein the recent, repeated consumption of a specific food decreases its pleasantness or palatability, while that of foods with relatively novel features remains stable. Although SSS was conceptualized decades ago, its underlying psychological components and its neural basis still require further investigation.As part of the mesolimbic dopamine system, dopamine release in the Nucleus Accumbens (NAc) is critical for processing natural rewards, including palatable foods. In relation to novelty and familiarity, prior literature suggests that dopamine in the NAc shell, but not the NAc core, is preferentially elevated by unfamiliar palatable food rewards and responds less to familiar ones. However, direct evidence remains limited regarding how dopamine signaling across the NAc shell and core relates to the specific process of sensory-specific satiety.In this study, we conducted diverse behavioral experiments demonstrating that variables such as repetition, recency, and food similarity generate noticeable reward devaluation. Moreover, utilizing fiber photometry based on these behavioral phenotypes, we monitored real-time dopamine release within the NAc core and shell subregions. Our data reveal how dopamine signals change dynamically as reward devaluation progresses, and specifically how these signaling patterns differ between the NAc core and shell.

Disclosures: Y. Lee: None. **Y. Kim:** None. **H. Choi:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

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Program #/Poster #: PSTR069.09/HH6

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Selective Deletion of a Glutamate Transporter, EAAT3, in Dopaminergic Neurons Alters Working Memory and Motivated Behaviors in Rats

Authors: *L. MITCHELL, S. G. AMARA, M. HU;
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Abstract: The excitatory amino acid transporter 3, EAAT3, is a neuronal glutamate transporter responsible for the clearance of extracellular glutamate from the perisynaptic space. Previous work from our lab has demonstrated that amphetamine enhances endocytosis of EAAT3 from the plasma membrane in midbrain dopamine (DA) neurons, suggesting a role for EAAT3 in the regulation of dopaminergic signaling. Amphetamine is a widely prescribed pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental disorder characterized by impairments in attention, motivation, and working memory. To further assess the role of EAAT3 in DA neurons, floxed EAAT3 rats (control) were crossed with DAT-Cre rats, generating a rat model in which EAAT3 was selectively deleted in DA neurons (EAAT3 DAT KO). The behavioral phenotype of EAAT3 DAT KO rats was examined using the open field (OF) test, radial arm maze (RAM), progressive ratio (PR) test, and cognitive touchscreen test (CTT). Control rats exhibited a robust increase in locomotor activity following amphetamine

administration during the OF test, while the response in EAAT3 DAT KO rats was significantly attenuated. In the RAM, EAAT3 DAT KO rats demonstrated impaired working memory, as evidenced by increases in revisit errors and task completion time. Furthermore, preliminary data from the PR test and the CTT suggest a lowered motivational breakpoint and altered cognition, respectively, in EAAT3 DAT KO rats. Taken together, these results demonstrate a crucial role for EAAT3 within DA neurons in mediating behavioral responses to amphetamine and supporting DA neuron-dependent cognitive and motivational processes, suggesting that impaired EAAT3 signaling may underlie deficits observed across neuropsychiatric disorders, including ADHD. Future investigation into attentional maintenance and impulsivity through the 5-choice serial reaction time task will further elucidate the potential link between EAAT3 in DA neurons and ADHD-related phenotypes.

Disclosures: L. Mitchell: None. **S.G. Amara:** None. **M. Hu:** None.

Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Eye Institute Intramural Research Program

Title: Tracking changes in dopamine and behavior during visual discrimination learning in mice

Authors: *C. QUAIA[1], K. ELLIOTT[2], K. K. COVER[3], R. J. KRAUZLIS[1];
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Abstract: Much of what we know about neuronal processing has been learned by measuring brain signals in well-trained subjects. Recently, however, there has been growing interest in tracking changes in neural signals as animals learn. Because learning is not a monolithic process, determining when a specific neural signal changes relative to behavioral signatures of learning can strongly constrain circuit theories of learning. We recorded dopamine release (via the dLight1.3b dopamine sensor) in the nucleus accumbens (NAc) of six C57BL/6J wild-type mice (3 males, 3 females). Mice ran on a wheel while facing two monitors. On each trial, one of two visual stimuli, a vertical or horizontal square-wave grating, was presented in a circular aperture on one monitor (with monitor side randomized across animals). One stimulus (target) was associated with reward, whereas the other (foil) was not. On target trials, reward was delivered after the first lick produced 1-3 s after stimulus onset; on foil trials, reward was never delivered. Each daily session consisted of ~100 trials, with target and foil trials pseudo-randomly interleaved. Mice quickly learned to lick for reward but initially licked indiscriminately after either stimulus. Over time, their licking became stimulus selective, with licking after foil stimuli reduced and eventually nearly eliminated. Stimulus dependent changes in running behavior were also observed. Throughout learning, we monitored dopamine release in NAc using fiber

photometry. Dopamine responses following the onset of target and foil stimuli were similar early in training and became significantly different when behavioral discrimination emerged, at least when evaluated at the session level. Accordingly, mice that exhibited behavioral changes sooner also showed dopamine changes sooner, and vice versa. We fit a GLM model to the data, using as regressors visual events, reward acquisition, licking, speed and acceleration, and found that we could predict quite well (r^2 between 0.2 and 0.6 across mice) dopamine release in the epoch containing stimulus onset and reward delivery (or omission), but much less so in the rest of the trial (r^2: 0.1-0.2), where large dopamine bursts were nonetheless frequent.

Disclosures: C. Quaia: None. **K. Elliott:** None. **K.K. Cover:** None. **R.J. Krauzlis:** None.

Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH/NINDS Grant 2RFNS023945-28

Title: Cholinergic Modulation of Orbitofrontal Cortex (OFC) Subregions in Value-Based Decision-Making

Authors: *A. VIVEK[1], M. E. LIBERADOR DOS SANTOS NUNES[2], L. ZABORSZKY[3]; [1]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ. Newark, Newark, NJ; [2]Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ., Hoboken, NJ; [3]Neurosci., Rutgers The State Univ. of New Jersey, Newark, NJ

Abstract: The orbitofrontal cortex (OFC) supports flexible decision-making through functionally specialized subregions: the lateral orbital area (LO) mediates reversal learning, the ventral orbital area (VO) supports outcome devaluation, and the medial orbital area (MO) regulates risk-based choice. Although cholinergic input from the nucleus basalis of Meynert (NBM) broadly modulates OFC function, whether distinct NBM projection pathways differentially support these subregion-specific behaviors remains unknown. To address this, adult male and female Long-Evans rats (n = 20M, 20F) were trained on three touchscreen-based paradigms designed to selectively engage LO, VO, and MO function: spatial reversal learning, reward devaluation, and risk-based decision-making. Behavioral validation confirmed that animals reliably acquired all three tasks, reaching the 70% correct criterion within 15 sessions, demonstrating significant devaluation sensitivity, and exhibiting probability-dependent risk preferences consistent with prior reports. These results confirm task sensitivity and establish the behavioral baseline for subsequent circuit manipulations. Intersectional viral ablation of NBM→OFC cholinergic projections is currently underway, combining retrograde AAV-Cre delivery to OFC with Cre-dependent caspase expression in NBM to selectively eliminate OFC-projecting cholinergic neurons while sparing projections to other targets. We predict that ablation

will impair reversal learning, devaluation sensitivity, and risk-based choice while leaving basic acquisition and reward sensitivity intact, providing the first causal evidence that topographically organized NBM→OFC cholinergic pathways differentially support distinct modes of adaptive decision-making.

Disclosures: A. Vivek: None. **M.E. Liberador Dos Santos Nunes:** None. **L. Zaborszky:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant 5R01DA053208

Title: The role of ventral tegmental area populations in ventral pallidum cue evoked activity

Authors: *S. WEIR, J. M. RICHARD;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: The ventral pallidum (VP) is a region of the basal forebrain that is critical for normal behavioral responses to reward-paired cues, and the majority of VP neurons respond to cues associated with reward. On average these cue-evoked responses precede similar signals in the nucleus accumbens (NAc) and indeed continue to occur even when ipsilateral or contralateral NAc cue responses are pharmacologically disrupted, indicating that the NAc is unlikely to be the sole source of these cue responses. However, it is still unclear what exact inputs to the VP facilitate this cue-evoked activity. One likely candidate is the ventral tegmental area (VTA). This region of the midbrain is known for sending dopaminergic projections to multiple regions in the mesolimbic dopamine system including the VP with these dopamine neurons having been repeatedly shown to play a crucial role in associative learning. The VTA also contains a population of GABAergic neurons which directly project to the VP among other structures and have been similarly shown to have a distinct yet important role in cue-reward learning. In the present study we sought to test the role of these two populations of VTA neurons in facilitating cue-evoked responses in the VP. Long-evans rats were first trained on a Pavlovian task to discriminate between a reward-predictive cue and a non-reward-predictive cue. We then utilized chemogenetics along with *in vivo* electrophysiology to test whether unilateral inhibition of VTA dopamine or GABA neurons impacted ipsilateral VP cue responses. We found a population of neurons in the VP that respond to reward-predictive cues and determined that these cue responses encode aspects of behavioral responding including entry into the reward port, proximity to the port, and latency to enter the port. Inhibition of the VTA GABAergic neurons increased the baseline firing rate of VP neurons but had no effect on the cue-responsivity of VP neurons. In contrast, inhibition of VTA dopamine neurons had no effect on baseline VP activity

but significantly decreased the strength of cue-evoked responses. This data presents preliminary evidence that VTA dopamine neurons contribute to VP cue-evoked activity.

Disclosures: S. Weir: None. **J.M. Richard:** None.

Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

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Program #/Poster #: PSTR069.13/HH10

Topic: H.02. Reward and Appetitive Learning and Memory

Support: RO1 MH129370

Title: Investigating the role of ventral pallidum dopamine signaling in reinforcement learning

Authors: *J. WELLS[1], B. T. SAUNDERS[2], J. M. RICHARD[2], A. R. WOLFF[2];
[1]Neurosci., Univ. of Minnesota (UMN), MINNEAPOLIS, MN; [2]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Dopamine (DA) neurons in the ventral tegmental area (VTA) play an important role in motivation, learning, and decision making, with unique functions assigned to populations based on their projection target. One dopamine pathway that has received little attention is the projection to the ventral pallidum (VP). The VP is involved in behavioral vigor and motivation, and neurons there strongly encode reward prediction errors (RPE). While dopaminergic projections from the VTA to the VP are established anatomically, their role in reinforcement and learning processes remain unknown. To assess this, we used an optogenetic intracranial self stimulation (ICSS) procedure. ChR2 was expressed in dopamine neurons in the VTA using TH-cre rats, and an optic fiber was placed over the DA neuron terminals in the VP. Rats were then given the opportunity to nose poke for laser stimulation. We found that VP DA terminal activation supported robust self stimulation behavior, which scaled in intensity as the stimulation frequency was increased. Stimulation seeking was relatively inflexible, however, as increasing the response ratio from 1 to 3 resulted in a complete lack of responding. Together, these results indicate that VP dopamine signal reinforcement to support learning simple action-outcome associations. In additional studies, we are probing local VP DA dynamics, using fiber photometry with the dLight sensor to test the hypothesis that DA in the VP encodes cues and reward expectation in a manner consistent with striatal RPE signaling.

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Poster

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Title: Nucleus accumbens dopamine responses to salient events reflect context-dependent behavioral significance

Authors: *R. YAMAKI[1], R. IIZUKA[1], T. I. SHIRAMATSU[1], M. NAKASHIMA[1,2], Y. IKEGAYA[1,3,4], H. TAKAHASHI[1,5];
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Abstract: Nucleus accumbens (NAc) dopamine (DA) is known to respond to salient events, but the computational and functional role of this response remains unclear. Given that NAc DA responses to salient events have been linked to attention and behavior, they may not simply reflect stimulus salience itself, but may reflect the utility of allocating resources for attention and action to an event, given the current situation. We therefore hypothesized that NAc DA responses to salient events are modulated by both stimulus salience and contextual importance. We expressed GRAB-DA2m in the NAc core of male Wistar rats and recorded DA signals with fiber photometry during a reward task (n=6) or fear conditioning (n=3). We used tasks in which specific auditory oddball sequences predicted subsequent reward or shock outcomes, allowing us to manipulate stimulus salience and contextual importance simultaneously. In both the reward task and fear conditioning, positive NAc core DA responses following event onset became larger when the context predicted more behaviorally important outcomes and when the stimulus was deviant. The difference between deviant and standard responses also increased with contextual importance, indicating that contextual importance and stimulus salience shaped NAc DA responses in an interactive, rather than purely additive, manner. In the reward task, we also examined the relationship between DA responses and head rotation, an orienting response thought to reflect attention to salient stimuli. We grouped CS+ deviant events according to head rotation magnitude and found that larger rotations were weakly associated with larger NAc core DA responses. By contrast, gross movement measures such as head speed showed no comparable relationship, suggesting that these DA responses were not simply explained by movement magnitude, but may be related to attention and behavioral regulation. Together, these results suggest that NAc core DA responses to salient events integrate contextual importance and stimulus salience to reflect the behavioral significance of events for allocating resources to attention and action.

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Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: Cue-evoked acetylcholine signaling in nucleus accumbens tracks discounted reward value and modulates delay discounting

Authors: J. CAVALLARO[1], ***D. R. ZUELKE**[2], R. SALAZAR[1], C. M. MAYSONET[1], R. SETARA[1], G. JAMMAR[1], E. F. GALLO[1];
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Abstract: Excessive impulsive choice, the preference for small, short-term rewards over larger, long-term rewards, is a prominent feature of neuropsychiatric and substance use disorders. While nucleus accumbens (NAc) dopamine signaling is implicated in impulsive choice, how it exerts its influence over striatal microcircuits to shape this behavior remains unresolved. We previously showed that dopamine D2 receptors on NAc cholinergic interneurons (CINs) promote impulsive choice, suggesting a key role for acetylcholine (ACh) signaling. However, whether NAc ACh tracks reward value and temporal cost and modulates delay-based choices is unknown. Here, we delivered an adeno-associated virus (AAV) expressing the ACh sensor $GRAB_{ACh3.0}$, and implanted an optic fiber in the NAc of adult male and female ChAT-Cre mice. This enabled fiber photometry analysis of ACh signals in the NAc in a delay discounting (DD) task that measures the choice between a small, immediate reward or a 3X larger reward presented at increasing delays. Sessions consisted of forced trials, presenting each option in isolation, followed by free choice trials, where both options were available. Trials began with a 5-s light cue above the levers prior to lever extension. Because predictive cues elicit multiphasic CIN firing and help evaluate different outcomes, we analyzed ACh signals as time-locked events aligned to the cue onset. We first measured “small” and “large” cue responses in forced trials of the initial no-delay training phase. We found a transient increase, followed by a sustained dip, in ACh for both cues. With training, there was a selective increase in the magnitude of the dip evoked by the large cue, matching the growing preference for the large reward. Increasing delays to the large reward following the lever press significantly attenuated the ACh dip evoked by the large cue, mirroring the behavioral shift towards the small, immediate reward. We also found a significant correlation between cue-evoked ACh dip size in forced trials and large reward preference in choice trials. We hypothesized that if the ACh dip size is involved in preserving the cue value representation across delays, then enlarging the cue-evoked dips for the large option should decrease DD. To this end, we expressed eNpHR3.0 or mCherry in NAc CINs and optogenetically inhibited CIN activity during large cues in forced trials. This significantly reduced the delay-dependent bias towards the small, immediate option, consistent with decreased impulsive choice. Together, our

findings suggest that NAc ACh dips track the learned and temporally-discounted value of reward-predictive cues, enabling cues to guide choices involving delays.

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Poster

PSTR069: Dopamine in Action: Learning, Value, and Behavioral Flexibility

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR069.16/HH13

Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Natural Science Foundation of China (No. 81971245, 82501790, 82471511)
the MOE Frontiers Science Center for Brain Science & Brain-Machine Integration, Zhejiang University

Title: Neural Dissociation of Digital Rewards: Amygdala-Driven Short-Video Consumption vs. Dopaminergic Internet Gaming

Authors: *H. ZHOU[1], Z. YE[1], T. HONG[1], C. GAO[1], R. WANG[1], C. SU[1], F. GENG[1], Q. HE[2], Y. HU[1];
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Abstract: While excessive short-form video consumption and internet gaming both manifest as addiction-like behaviors, they likely stem from distinct neural mechanisms. Short videos promote a passive state of immediate gratification, whereas gaming is a goal-directed activity demanding continuous cognitive resource. However, direct neurobiological evidence supporting this dissociation is lacking. We conducted two ecologically valid fMRI experiments using a 3T scanner to compare the neural signatures of autonomous video viewing and competitive gaming. In the short-video task, 62 participants (age = 23.10 ± 2.46) autonomously watched or switched between clips. In the gaming task, 32 participants (age =22.84 ± 2.03) played a discontinuous real-time strategy game. Data were analyzed using block-wise and event-related general linear models. Representational similarity analysis (RSA) with a 5000-permutation test was performed to compare regional activation patterns against a predefined reward signature and neurotransmitter receptor density maps (e.g., Cannabinoid receptor 1, CB_1; μ-opioid receptor, MOR). Results revealed divergent neural pathways. Video blocks significantly activated the amygdala ($t_{(61)} = 10.03$, $p < 0.001$) and substantia nigra (SN; $t_{(61)} = 5.70$, $p < 0.001$), but not the ventral tegmental area (VTA) or nucleus accumbens (NAcc). Fully watched “Like” videos elicited significantly higher amygdala activation than skipped “Dislike” videos ($t_{(61)} = 3.85$, $p < 0.001$). RSA demonstrated that the amygdala’s activation pattern under the “Like” condition was significantly more similar to the reward signature ($p_{perm} < 0.001$), as well as CB_1 and MOR distribution patterns ($p_{perm} < 0.001$), than the “Dislike” condition. Conversely, gaming blocks

primarily activated the SN ($t_{(31)} = 5.19$, $p < 0.001$). Event-related GLMs showed that active "Fight" events (active engagement moments) elicited significantly greater SN activation than simple "Move" events (purposeful movement and environmental surveillance, $t_{(31)} = 3.38$, $p = 0.002$). Under the "Fight" condition, the NAcc activation pattern was significantly more similar to the reward signature than during the "Move" condition ($p_{perm} < 0.001$). Furthermore, prefrontal cognitive control regions exhibited inhibition during video viewing but marked activation during gaming ($p < 0.01$). These findings suggest competitive gaming heavily recruits a traditional goal-directed, dopaminergic reward pathway requiring high cognitive control, whereas the reinforcing nature of short-video viewing leverages an amygdala-centered, CB_1- and MOR-mediated hedonic loop for low-demand digital rewards.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

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Program #/Poster #: PSTR070.01/HH14

Topic: H.03. Motivation

Support: NIH Grant R01-MH133123

Title: Corticolimbic Regulation of Partner-Seeking After Pair-Bond Loss in Prairie Voles

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Abstract: Social loss, or the permanent loss of a social relationship, can produce a persistent sense of "yearning" for the lost partner and manifest as increased motivation to seek partner-associated cues. In humans, limbic brain regions, such as the anterior cingulate cortex (ACC) and ventral tegmental area (VTA), activate in response to partner-related cues, and their activity correlates with yearning intensity. However, it is not clear if ACC and VTA directly regulate response to partner-related cues during social loss. Our research has used the socially monogamous prairie vole (*Microtus ochrogaster*) as a model species to study the neurobiology of partner loss. Previous work on receptor expression and behavioral changes in the loss state suggests preoccupation with partner cues may be driven by altered dopamine signaling in the ACC. Our current work further probed cellular and signaling changes using pharmacology and RNAseq analysis in the ACC and VTA. Voles were paired with an opposite-sex partner for one week and pair-bond (PB) status was assessed via partner-preference test after which loss groups were single-housed for one week. A cohort of these animals were bilaterally cannulated into either the ACC or VTA prior to pairing, allowing for site-specific infusion of dopamine receptor

antagonists (ACC), glutamate receptor agonists (VTA), or vehicle (both) immediately prior to an odor preference test between partner and food scented bedding on the seventh day of loss. Time spent in proximity and actively investigating scented bedding was quantified and analyzed. While PB animals that lost a partner spent significantly more time investigating partner odors than PB intact and non-bonded loss groups, nonspecific dopamine antagonism and specific antagonism of DRD1 was sufficient to reduce partner-seeking behavior in voles that lost a PB partner. Additionally, agonism of glutamate receptors in the VTA reduced partner-seeking. To identify regional changes to gene expression, punches of male voles were taken in the ACC and VTA and processed for Bulk RNAseq analysis. These results showed significant differentially expressed genes when comparing intact to loss groups. Genes related to altered stress and immune response, synaptic plasticity, and glutamatergic signaling were noted. This is the first work to identify a causal link between signaling in the ACC and VTA and increased partner-seeking after social loss. RNAseq findings have uncovered potential new molecular mechanisms to explore driving altered behavior and biology during loss. Future work will focus on characterizing potential physical and functional connections between these regions.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR070.02/HH15

Topic: H.03. Motivation

Title: Human neural representation of effort and reward during a progressive ratio task

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Abstract: Motivated behaviors require the constant evaluation of potential rewards against the effort required to obtain them. Impairments in motivation are associated with severe disabilities and neuropsychiatric disorders with no effective therapeutic interventions. The progressive ratio (PRT) task is a well-validated translational paradigm for quantifying the willingness to escalate effort exertion to obtain a reward until a subject voluntarily terminates the task, yielding a motivational drive index called the breakpoint. Scalp electroencephalography (EEG) studies during the PRT reveal reward-locked signals increase with effort demands. Functional MRI studies implicate the ventromedial prefrontal cortex and ventral striatum in representing net value. Human intracranial recordings suggest high-frequency activity encoding of subjective value and reward prediction signals in the orbitofrontal cortex, amygdala, and hippocampus. In spite of these findings, the neural dynamics of effort-based motivation across escalating ratio demands is poorly understood. Here, to examine how human neural activity evolves during an

effort-based decision task, we administered a computerized PRT in 24 epilepsy patients implanted with depth electrodes undergoing intracranial EEG. Participants completed up to 1600 trials (comparison of two random numbers) to earn a monetary reward while the required effort escalated across successive sets of trials. We observed a wide range of behavior performance as measured by the breakpoint (-0.6 to 1). Within-set quit probability scaled with effort but was largely independent of reward magnitude, response time, and accuracy. Increased effort requirement was associated with decreased hippocampal and OFC gamma power and increased amygdala alpha power, implicating tracking of subjective value by the limbic system. Additionally, limbic and prefrontal regions simultaneously encode effort cost and reward value within the first 600 milliseconds of trial onset: OFC high-gamma preferentially encodes reward and dACC alpha encodes effort, implicating anatomically-segregated cost-reward computations instead of a spatially-nonspecific value signal. Through intracranial recordings during an effort-escalating PRT, we demonstrate the human brain evaluates decisions through parallel but anatomically distinct cost and reward circuits. By localizing these dissociable signals to specific structures and frequencies, our findings identify candidate neural substrates of effort-based motivation.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

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Program #/Poster #: PSTR070.03/HH16

Topic: H.03. Motivation

Title: Neural integration-segregation switching during task anticipation reveals a neurophysiological signature of grit

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Abstract: Grit, the capacity to sustain effort toward difficult goals, is studied as a personality trait, but its task-evoked neurophysiological basis remains unclear. We conceptualized grit as approach-related motivation and adaptive engagement, indexed by frontal alpha asymmetry (FAA) and task-anticipatory integration-segregation switching. 31 students performed a 10-disk Tower of Hanoi task requiring 1023 moves. Participants were instructed to complete the task without time information and to raise their hand only if they wished to stop. Those who remained engaged for 30 min were classified as persistent (n=23), and those who stopped as quitters (n=8).

64-channel EEG was recorded during 5-min pre-task rest and 1-min task anticipation. After Schaefer 100-based source estimation, alpha/gamma degree, clustering coefficient (CC), and amplitude-envelope connectivity were calculated; participation coefficient (PC) was computed from Yeo 7 networks. FAA was calculated as ln(F4)−ln(F3). Group differences were tested using Bayesian tests, FDR-corrected permutation tests, and NBS. Discriminative relevance was evaluated using nested leave-one-out machine learning with inner repeated stratified cross-validation, SVM/LASSO, train-only preprocessing/thresholding, DeLong CIs, and SHAP. Groups did not differ in demographics, questionnaires, or regional power. Quitters showed increased alpha-CC in dorsal-attention/limbic regions and increased gamma-degree in sensorimotor and right prefrontal control regions during task anticipation and change. At the network level, quitters showed increased gamma-PC in dorsal-attention/control networks and alpha-PC in the limbic network, suggesting coexistence of local segregation and hyper-integration. NBS showed stronger resting frontal gamma connectivity in quitters, whereas persistent participants showed greater occipital gamma-connectivity increases during task anticipation. FAA was lower in quitters during task anticipation/change. Machine-learning performance was low at rest (accuracy=51.6%, AUC=0.652 [0.401-0.903]) but high during task anticipation (90.3%, AUC=0.967 [0.902-1.000]) and change (93.5%, AUC=0.978 [0.931-1.000]). Selected features were dominated by integration-segregation indices: right prefrontal gamma-degree, alpha-CC, gamma-PC, and FAA. These results suggest that grit emerges during task confrontation as flexible integration-segregation switching rather than as a static personality or resting-state feature. Task-anticipatory network reconfiguration, with frontal motivational asymmetry, may constitute a neurophysiological signature of grit.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.04/HH17

Topic: H.03. Motivation

Title: Motivational profiles and adaptive gaming-related functioning: A structural equation modeling study

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Abstract: Background: Research on gaming-related difficulties often assumes that greater gaming involvement reflects greater risk. However, gaming is a heterogeneous activity, and motivational factors may help explain why some individuals experience difficulties whereas others report adaptive outcomes despite similar levels of engagement. This study examined the

relationship between gaming motivations and a latent construct reflecting adaptive gaming-related functioning. **Methods**: Participants were drawn from a community sample of 974 adults. Analyses were restricted to individuals who reported playing video games (n = 779; 38% women; Mage = 25.40 years, SD = 8.15). The newly developed Gaming Disorder Scale was scored using a bidirectional format in which higher scores reflect strengths and adaptive regulation, whereas lower scores reflect difficulties. Confirmatory factor analyses compared alternative measurement models, including bifactor and second-order structures. Structural equation models were estimated using robust maximum likelihood (MLR) to account for non-normality, with gaming motivations predicting a higher-order gaming adaptation factor composed of loss-of-control regulation, mental well-being, and social well-being dimensions. **Results**: The second-order model demonstrated acceptable fit (CFI = .958, TLI = .943, RMSEA = .054, SRMR = .035), supporting the presence of a general gaming adaptation factor underlying the three domains. A bifactor model produced inadmissible solutions and was not retained. In the structural model, intrinsic motivation positively predicted gaming adaptation ($\beta = .28$, $p = .001$), whereas competitiveness showed a negative association ($\beta = -.24$, $p = .030$). Extrinsic motivation was not significantly related to gaming adaptation ($\beta = -.06$, $p = .49$). Notably, when motivations were examined individually, none significantly predicted gaming adaptation, suggesting that observed effects emerged only after accounting for variance shared across motivational dimensions. Conclusions: Findings suggest that gaming-related functioning is better understood through motivational profiles rather than gaming involvement alone. Individuals who play primarily for intrinsic enjoyment may represent a distinct profile from those whose engagement is driven by competitive goals. These results highlight the importance of distinguishing among gamers when evaluating risk and adaptation, challenging simplistic assumptions that gaming behavior can be understood solely in terms of frequency or intensity of play.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

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Title: A neuroeconomic approach to study deliberative prosocial decision-making in mice

Authors: *A. N. RAMIREZ[1], P. DAVIS[2], M. L. KONDEPUDY[2], H. E. KWA[2], J. CAI[2], N. JAHAN[2], R. DURAND-DE CUTTOLI[3], B. M. SWEIS[4];
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Abstract: Prosocial behaviors aim to benefit another, sometimes at a cost to oneself. Recent studies have reported mice are capable of allocating resources to others; however, the neural mechanisms underlying cost-benefit decision processes when considering the needs of another remains underexplored in rodent models.
I developed a novel foraging task to study prosocial decision-making in mice. An actor mouse navigates a spatial arena with four distinct reward zones ("restaurants") while on a limited time budget, foraging for their main source of food. Two of the four restaurants feed both the actor and a recipient mouse, while the other two feed only the actor. One of each of these restaurants provides a highly palatable flavor while the other provides a plain flavored pellet. Reward costs vary in the form of delays that mice must wait out to earn food that, importantly, are cued trial-by-trial by the pitch of a tone. Each restaurant is divided into a discrete Offer Zone and Wait Zone that task the mice with first making an initial skip vs. enter decision followed by a secondary quit vs. continue waiting out the delay re-evaluative choice.
Overall, actors displayed a significant prosocial preference for earning at restaurants that allocated rewards to both mice while also exhibiting subjective flavor preferences. Mice with higher prosocial preferences also show differential decision-making strategies compared to mice with lower prosocial preferences. In the Offer Zone, high prosocial mice accept offers of all costs at "both" restaurants more often than "self" restaurants. In the Wait Zone, high prosocial mice show an increased willingness to wait for rewards for both mice rather than only self distinctly in mid-range offers. This suggests that initial commitments to prosocial behavior in the Offer Zone and actualized prosocial behavior in the Wait Zone may rely on separate action-selection planning and re-evaluative processes in the brain that differentially calculate prosocial value.
Preliminary screening for cFos activation revealed that actors with a recipient present have more cFos+ cells in the amygdala (AMG) than actor mice without a recipient but show similar numbers of cFos+ cells in the medial prefrontal cortex (mPFC), suggesting the AMG may be a key driver of dissociable prosocial valuation algorithms on this task.
These results suggest mice are capable of modulating foraging strategies to benefit a conspecific. Differences in prosocial behavior in the Offer Zone and Wait Zone indicate that computations to benefit another likely rely on separate circuitry, including the AMG vs. mPFC, and could reveal unique points of vulnerability in dysfunctional prosocial behavior.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

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BBRF NARSAD YI Grant 31140
FBI Scholars Award

Title: The ventral tegmental area and dorsal raphe nucleus control neuroeconomically distinct choice behavior

Authors: H. KWA[1], N. JAHAN[1], P. DAVIS[1], M. KONDEPUDY[1], A. RAMIREZ[2], E. ANDRAKA[2], H. L. ROSENBLUM[2], S. PEDERSEN[1], R. DURAND-DE CUTTOLI[2], ***B. M. SWEIS**[3];
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Abstract: How the brain makes choices depends on multiple decision-making processes. Dopamine and serotonin are both implicated in motivated choice, yet their distinct roles in separable decision computations remain poorly understood.
Here, we interrogated how the ventral tegmental area (VTA) and dorsal raphe nucleus (DRN) contribute to distinct choice policies in mice tested on the neuroeconomic foraging paradigm, Restaurant Row. On this task, mice operate under a limited time budget to forage for food rewards of varying costs (1-30s delays cued by tone pitch) and subjective value (unique flavors). Each trial unfolded across two sequential decision stages: an offer zone, where mice made deliberative accept vs. reject decisions, and a wait zone, where mice made re-evaluative stay vs. quit decisions during tone countdowns.
We transfected the VTA or DRN of 44 male Swiss Webster mice with adeno-associated viruses expressing hM3Dq, hM4Di, or no chemogenetic receptors under the synapsin promoter, enabling bidirectional manipulation of neural activity via clozapine-N-oxide or saline administration.
All groups retained sensitivity to offer cost without changes in overall task engagement, locomotor speed, or consumption behavior. Both regions had shared effects on offer zone acceptance: inhibition of the VTA or DRN increased acceptance of high-cost offers, while excitation of both decreased acceptance of low-cost offers. The two systems diverged, however, in the wait zone. VTA excitation decreased willingness to wait out delays, while DRN excitation increased it. Examining the basis of this divergence, we found that sunk cost sensitivity—the propensity to continue waiting as a function of time already spent in the wait zone—was selectively reduced in the DRN excitation group. The combination of increased willingness to wait alongside decreased sunk cost sensitivity suggests that DRN activity shifts valuation toward prospective reward, making animals more forward-looking while discounting past expenditures.
Choice latency in the wait zone was unaffected across groups; in the offer zone, latency was increased only by excitation, with VTA excitation slowing both accept and skip decisions and DRN excitation slowing only accept decisions, consistent with a selective role of the DRN in

evaluating reward approach rather than general response timing.
Together, these results indicate that dopamine and serotonin systems exert distinguishable influences on choice behavior: shared effects on cost-sensitive acceptance policies, but opposing effects on persistence during reward anticipation—effects that map onto separable computational stages of the decision stream.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

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Program #/Poster #: PSTR070.07/HH20

Topic: H.03. Motivation

Support: NIH DIRP ZIAMH002797

Title: Motivation and licking patterns in a Go/no-Go task in mice and their relation to cortical activity assessed using 2-photon imaging

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Abstract: Internal states dramatically influence behavior and can mask the expression of learning. While task performance is often used to evaluate knowledge, behavioral outputs and cortical dynamics are heavily modulated by motivation. Here, we investigated how motivational states, licking patterns, and cortical network activity interfere over days during a lick/no-lick visual location discrimination task in water-restricted animals. During this task, mice were head-fixed at a 30-degree angle to a monitor that displayed a Gabor patch for “trials” up to 2 sec. Mice received a water reward upon licking when the stimulus was at its “target” position in the center of the monitor; they received an air puff to the outer ear as punishment if they licked when the stimulus was in a “non-target” position. For n=13 animals (7 with a sound played at the beginning of each trial, and 6 without), we used two-photon in vivo calcium imaging to record neuronal activity in the cortex 5 min prior to the task, during the 40 min session, and 5 min after. Inter-trial intervals had varying lengths, depending on whether the mouse continued to lick after the visual signal disappeared and depending on the trial outcome. Licking during 0.5 sec after the visual signal appeared was not rewarded or punished (buffer period). We trained mice for 19-45 days. Parameters like animal relative weight and total licking activity were used to estimate motivation level. For behavior pattern analysis, we investigate licking distribution during trials and consecutive inter-trial intervals, focusing on the presence of bouts versus separate licks and

indicators of learning/not learning (licking only during buffer period, hanging water reward). Our analysis of licking structures showed that lick pattern distributions changed depending on motivation. We examined firing rate, mean cell-to-cell correlations, clustering coefficient, and network criticality utilizing the chi_sh metric to characterize cortical activity state for 3 mice. Preliminary analysis revealed that mean cell-to-cell correlations 5 minutes before the task positively correlated with both total lick numbers and discrimination performance, while negatively correlating with the number of missed trials. During the task, cell-to-cell correlations and mean spike rates positively tracked total lick numbers. The network criticality parameter chi_sh positively correlated with total licks both before and during the task. These metrics identify specific cortical signatures that track and predict behavioral outcomes and performance.

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Poster

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Title: Toward a cross-species model of social-cognitive maps

Authors: *E. ANDRAKA[1], D. SCHILLER[1], B. M. SWEIS[2];
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Abstract: Prior studies have revealed that the human hippocampus and posterior medial cortex track social relationships along orthogonal dimensions of affiliation (amicable vs. antagonistic) and power (influential vs. uninfluential). This information is thought to contribute to the organization of a social-cognitive map that guides behavior, with growing evidence of its alteration in conditions that span mood, developmental, and personality disorders. Causally interrogating such pathways with temporal- and projection-specificity during social choice is challenging in humans. To this end, I adapted the food-based neuroeconomic task, “Restaurant Row”, into a social decision-making task in which mice spatially forage for social interactions

rather than food rewards. In this task, socially isolated mice forage for their sole source of daily social contact with four conspecifics who differ in social relatedness (social identity based on familiarity and tube test competition scores). Cost to access social interactions with each conspecific vary in the form of cued delays (auditory tones). Thus, mice must learn to optimize social decision-making strategies amidst a changing economic landscape. To probe the effects of agentive, reciprocal task engagement on dynamic social behavior, we permitted some mice to forage for the same conspecifics who then on a subsequent session foraged for them in return, while restricting this ability in other mice who instead served only as actors or targets. I am currently analyzing data from a large-scale behavioral study (N=102, 51F) I conducted which validates that mice engage this task longitudinally, respond to changes in cost, distinguish object control from mouse stimuli, discriminate tone information at distinct choice points on a trial-by-trial basis, and vary in total interaction experience (but not actor-driven task engagement) due to the ability to switch actor-target roles. Preliminary analyses reveal tube test score-based differences in cost sensitivity during deliberative decision-making, which may highlight varied hippocampal recruitment across distinct identities. Further, we successfully recorded a dynamic range of task videos and ultrasonic vocalizations which could indicate interaction valence and help explain choice behavior (analysis of 120 total dyads with SLEAP and DeepSqueak platforms, respectively). This work sets the stage for applying cutting-edge circuit dissection tools to probe valuation algorithms influencing social choice, with the goal of advancing the understanding and development of new treatments for psychiatric disorders presenting with altered social cognition.

Disclosures: E. Andraka: None. **D. Schiller:** None. **B.M. Sweis:** None.

Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.09/HH22

Topic: H.03. Motivation

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Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Fellowship
Brain & Behavioral Foundation Young Investigator Award 32856
Leon Levy Foundation Neuroscience Fellowship
FBI Scholars Award
Animal Models for the Social Dimensions of Health and Aging Research Network Award
NIMH R01 MH120162
McKnight Memory and Cognitive Disorder Award

Title: Developing a task to probe how internal state changes affect hippocampal spatial codes

Authors: *H. L. ROSENBLUM, P. DAVIS, M. L. KONDEPUDY, H. E. KWA, D. J. CAI, B. M. SWEIS;
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Abstract: How do internal states change environmental representations in the hippocampus to support adaptive, goal-directed behavior? The hippocampus plays a key role in spatial memory and navigation, with place cells forming stable maps within a context but remapping across different contexts. Previous work indicates remapping also occurs across hunger versus thirst states, suggesting that internal states could function as distinct contexts that promote state-specific spatial maps. However, few studies have investigated how the hippocampus represents the same environment under multiple states (thirst, hunger) over time or the relationships between environmental features relevant for different states (water, food locations; reward magnitude). To investigate how internal states shape the organizing principles of hippocampal spatial representations, we designed a task where mice navigate through four interconnected rooms associated with food or water reward while food- or water-restricted. To probe how features of these rooms are represented across states, each room was associated with a low or high magnitude reward, which was delivered after the mouse occupied the room for 1 second. Across three behavioral cohorts (food/water alternation, food/water/ad lib alternation, and shuffled restriction sequences; N=18 C57BL/6 mice total, 9 female), we found that mice spent more time occupying rooms that corresponded to the restricted condition, which also scaled by reward magnitude. Mice also increased head entries into water reward sites and showed greater licking at the water ports on water restricted sessions compared to food restricted sessions. A fourth cohort of 3 mice completed the food/water/ad lib restriction timeline while simultaneously recording from dCA1 with miniature microscopes across 19 days. This approach allows the tracking of cells across multiple sessions and restriction states, which will be used to compare the stability of hippocampal spatial codes across same versus different states. To understand how increased reward cost may further impact choices across restriction states, we have also collected data from fixed cost (7.5-second delays prior to reward deliveries) and variable cost (delays sampled from a uniform distribution of 1-15 seconds) cohorts (N=10). These data indicate that willingness to wait for reward may also be modulated by reward magnitude and restriction state. Altogether, these behavioral experiments provide evidence that our task is sensitive to restriction state manipulations, which will be utilized to understand how internal factors shape hippocampal computations involved in flexible navigation.

Disclosures: H.L. Rosenblum: None. **P. Davis:** None. **M.L. Kondepudy:** None. **H.E. Kwa:** None. **D.J. Cai:** None. **B.M. Sweis:** None.

Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.10/HH23

Topic: H.03. Motivation

Support: NIH NIDA R15DA058186

Title: Reward Engagement Following Effort-Based Access to Drug and Social Rewards

Authors: *M. VANN-SCOTT[1], J. DAVIS[1], A. NAUHRIA[1], D. B. LESTER[2];
[2]Psychology Dept., [1]Univ. of Memphis, Memphis, TN

Abstract: Effort-based tasks assess the motivation to obtain rewards. The current study examined whether behaviors expressed during reward access were related to the effort animals were willing to exert to obtain those rewards. Male and female C57BL/6J were assigned to the following reward groups: cocaine (10 mg/kg, i.p.), familiar social interaction, novel social interaction, or no reward. Mice completed two sessions per day for up to 16 sessions in a weighted-door effort task, pushing a door of increasing weight (0-283g) to access the reward chamber. Once mice pushed the door for access into the reward chamber, they received the reward and remained in the reward chamber for 20 min. During this time, locomotor activity was assessed in the cocaine and no-reward groups, while the duration of social interaction was assessed in the familiar and novel social groups. Reward-chamber behaviors were not significantly correlated with breaking weight, defined as the maximum door weight successfully pushed to obtain the reward. Cocaine-rewarded mice exhibited greater locomotor activity than mice in the control (no reward) group, and mice in the familiar social interaction group exhibited longer durations of body contact than mice in the novel social interaction group. No significant sex differences were observed. These findings suggest that reward engagement and effort expenditure represent distinct aspects of reward processing.

Disclosures: M. Vann-Scott: None. **J. Davis:** None. **A. Nauhria:** None. **D.B. Lester:** None.

Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

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Topic: H.03. Motivation

Support: NIMH BRAINS R01 R01MH136230
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Seaver Foundation Fellowship
Brain & Behavioral Foundation Young Investigator Award 32856
Leon Levy Foundation Neuroscience Fellowship
FBI Scholars Award
Animal Models for the Social Dimensions of Health and Aging Research Network Award

Title: A neuroeconomic approach to understanding decision-making behavior in a mouse model of binge-eating disorder

Authors: *M. L. KONDEPUDY[1], P. DAVIS[1], H. E. KWA[1], N. JAHAN[1], J. SEO[1], N. AHMED[1], Z. HUSSAIN[1], R. DURAND-DE CUTTOLI[2], G. VOLOUDAKIS[1], B. M. SWEIS[1]; [1]Psychiatry, [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: How the brain makes choices depends on multiple decision-making algorithms. In binge-eating disorder, abnormal information processing associated with food rewards may manifest as complex alterations in dissociable drivers of value-based choice, extending beyond simple definitions of impulsivity. Here, we used a novel variant of our neuroeconomic foraging paradigm, Restaurant Row, that introduces competing diet types and food access times to probe binge-related decisions in a mouse model of binge-eating disorder. Mice had a limited daily time budget (1 hour) to forage among one of four restaurants for food rewards of varying costs (delays signaled by tone pitch, randomly selected on each trial from a range of offers that escalated stepwise across weeks of testing). Each trial began at a T-intersection (offer zone, OZ), where a tone sounded until mice turned left to skip or right to approach the reward site (wait zone, WZ). In the WZ, a tone countdown began cueing progress until either a secondary premature quit decision was made or mice waited the full delay to earn a reward. Rewards consisted of a mesh-covered cache of chow behind a door that was accessible for a fixed duration, with two restaurants offering 10s access and two offering 40s access. Two restaurants offered regular diet (RD) and two offered high-fat diet (HFD, 60% kcal from fat) caches. Prior to testing, two groups of female mice (N=12/group) received 5 weeks of intermittent home-cage HFD access (1 day/wk) with weekly injections of saline (iH-Sal) or iron dextran (iH-FeDx, 150mg/kg ip), an iron-overload manipulation motivated by human genetic data and independently validated to exacerbate binge-like feeding. Two additional groups received chronic HFD (cH) or served as regular-diet only controls (Con). Mice then underwent 30 days of Restaurant Row without food restriction. All mice acquired the task, increasing earnings based on diet type and access time. As mice transitioned to higher-cost environments, all groups except cH increased task engagement to forage for more offers. As OZ policies became more cost-sensitive, reaction times increased—particularly for skip decisions—except in both iH groups, who failed to develop this profile. iH-Sal, and more so iH-FeDx, showed sharp increases in WZ quitting at each cost transition, particularly in HFD restaurants, suggesting iH became increasingly accepting of offers they were unwilling to follow through on, separating initial choices in the OZ from actualized commitments in the WZ. These data reveal that a neuroeconomic framework can dissociate impulsive valuations during deliberation vs. re-evaluative choices that underlie binge-related decisions.

Disclosures: M.L. Kondepudy: None. **P. Davis:** None. **H.E. Kwa:** None. **N. Jahan:** None. **J. Seo:** None. **N. Ahmed:** None. **Z. Hussain:** None. **R. Durand-De Cuttoli:** None. **G. Voloudakis:** None. **B.M. Sweis:** None.

Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.12/HH25

Topic: H.03. Motivation

Support: NIMH BRAINS R01 R01MH136230
Burroughs Wellcome Fund Career Award for Medical Scientists
Seaver Foundation Fellowship
Brain & Behavioral Foundation Young Investigator Award 32856
Leon Levy Foundation Neuroscience Fellowship
FBI Scholars Award
Animal Models for the Social Dimensions of Health and Aging Research Network Award

Title: Characterizing the effects of GLP-1 agonists (semaglutide) on neuroeconomic decision-making behavior in a mouse model of binge eating disorder

Authors: *P. DAVIS[1], M. KONDEPUDY[2], H. KWA[2], N. JAHAN[2], J. SEO[2], N. AHMED[2], Z. HUSSAIN[2], R. DURAND-DE CUTTOLI[3], G. VOLOUDAKIS[5], B. M. SWEIS[4];
[2]Psychiatry, [3]Neurosci., [4]Psychiatry, Neurosci., [1]Icahn Sch. of Med. at Mount Sinai, New York, NY; [5]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: How the brain makes choices depends on multiple decision-making algorithms. In binge-eating disorder, abnormal food reward processing may manifest as complex alterations in dissociable drivers of value-based choice, extending beyond simple definitions of impulsivity. GLP-1 agonists including semaglutide are a promising option to curb craving and normalize maladaptive feeding, but how this drug engages decision-making processes remains underexplored.Here, we used a novel variant of our neuroeconomic foraging paradigm, Restaurant Row, that introduces competing diet types and food access times to probe binge-related decision-making in a mouse model of binge-eating disorder. Mice had a limited daily time budget (1 hour) to forage among one of four restaurants for food rewards of varying costs (delays signaled by tone pitch). Each trial began at a T-intersection, where a tone sounded until mice turned left to skip or right to approach the reward site. There, a tone countdown cued progress until a premature quit decision or full delay completion earned a reward: a cache of chow accessible for 10s or 40s depending on restaurant. Two restaurants offered regular diet (RD) and two offered high-fat diet (HFD, 60% kcal from fat) caches. Prior to testing, two groups of female mice (N=12/group) received 5 weeks of intermittent home-cage HFD access (1 day/wk) with weekly injections of saline (iH-Sal) or iron dextran (iH-FeDx, 150mg/kg ip), an iron-overload manipulation motivated by human genetic data and independently validated to exacerbate binge-like feeding. Two additional groups received chronic HFD (cH) or regular diet only (Con). Mice then underwent 30 days of Restaurant Row without food restriction. After training, mice underwent within-subjects testing: saline, then 10 daily doses of semaglutide (0.1mg/kg ip), then a 5-day washout.All groups showed weight loss on semaglutide. Only cH mice showed sustained weight loss (~10% bodyweight) across all 10 days; other groups showed only a transient drop (days 1-3) before renormalizing despite continued drug exposure, and cH bodyweight rebounded during washout. Critically, iH-FeDx mice showed the largest drug-induced suppression in rewards earned, most notably in HFD restaurants, despite remaining weight-neutral. These mice also showed the greatest modulation in reaction times, particularly increased for skip decisions—not explained by gross changes in locomotor activity. Together, these data suggest semaglutide may promote deliberative decision-making, whether by directly

engaging these processes or by suppressing competing systems (e.g., habitual control), thereby reducing compulsive-like feeding.

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Poster

PSTR070: Effort, Choice, Social Reward, and Neuroeconomic Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR070.13/HH26

Topic: H.03. Motivation

Support: NIH 7UH3NS103446-03
NIH 1R01MH124760-01A10

Title: Interim Analysis of BITES Trial: From Human Accumbens Biomarker Discovery to Responsive Deep Brain Stimulation Outcomes for Loss of Control Eating

Authors: *W. CHOI[1], L. QIU[1], N. VARDALAKIS[1], R. L. SEILHEIMER[4], I. CAJIGAS[1], B. PESARAN[2], K. W. SCANGOS[1], J. I. GOLD[3], C. H. HALPERN[1];
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Abstract: An early safety and feasibility trial (EFS, NCT03868670) was conducted using responsive deep brain stimulation (rDBS) of the nucleus accumbens (NAc) to ameliorate loss of control (LOC) eating in a small cohort of human subjects (N = 4) with treatment-resistant obesity. Here, we report an interim analysis of electrophysiological biomarker data from the ambulatory setting across the cohort and primary outcomes of this first-in-human NAc rDBS study. Ambulatory NAc intracranial recordings were acquired at participant-triggered or preset times during food preoccupation or rest in a six-month biomarker discovery phase and a one-year of stimulation phase. Primary outcomes included the number of LOC eating episodes and intervention-related adverse events. A largely conserved electrophysiological biomarker was identified across four participants in the ambulatory setting; low-frequency power (1-7 Hz) in the NAc increased in all participants during moments of food preoccupation vs. at rest (permutation test, $p<0.05$). rDBS has been activated in three of four participants and the low-frequency power was attenuated at a higher stimulation dose. A generalized mix-effect model fit demonstrated an inverse association (β =-0.25 [SE=0.018], -0.31 [0.056], and -0.11 [0.002], respectively with $p<0.001$) between the number of the low-frequency signal detection from the device and the stimulation does change. Moreover, Participants 1 and 2 experienced 75% and 73% decrease in the number of LOC eating episodes at the end of stimulation phase. Participant 3 experienced 95% decrease in LOC episodes after 6 months of stimulation and remains under evaluation. No serious adverse occurred and ~73% of reported adverse events were mild. This EFS provided a

novel platform for ambulatory biomarker discovery and insights into brain-based mechanisms of LOC eating. Moreover, NAc rDBS appears safe and feasible with preliminary efficacy in reducing LOC eating episodes.

Disclosures: W. Choi: None. **L. Qiu:** None. **N. Vardalakis:** None. **R.L. Seilheimer:** None. **I. Cajigas:** None. **B. Pesaran:** None. **K.W. Scangos:** None. **J.I. Gold:** None. **C.H. Halpern:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

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Program #/Poster #: PSTR071.01/HH27

Topic: H.02. Reward and Appetitive Learning and Memory

Support: SERB CRG/2020/004971
SERB CRG 2022/004795

Title: Metabolic state-dependent neuroadaptations in the nucleus accumbens drives reward sensitization

Authors: *V. A. BORADE[1], D. S. LONDHE[2], A. J. SAKHARKAR[1];
[1]Dept. of Biotech., Savitribai Phule Pune University, Pune, India, Pune, India; [2]Dept. of Biotech., Modern college of Arts, Sci. and Commerce, Pune, India

Abstract: Metabolic state affects reward processing in the brain. However, the underlying neuroadaptations in reward neurocircuitry due to feeding habits remain poorly understood. We investigated the significance of epigenetic changes driven by metabolic state such as food-restriction in reward sensitization. Adult male Wistar rats were subjected to 48 h food-restriction and assessed for reward seeking for sweet food pellets in nose-poke operant conditioning paradigm. Food-restriction increased tyrosine hydroxylase (TH) expression in the ventral tegmental area (VTA) and elevated Dopamine receptor 1 (D1R), Dopamine transporter (DAT), Brain derived neurotropic factor (BDNF), and cFOS expression in the nucleus accumbens (NAc). These findings posit enhanced dopaminergic activity in reward circuitry of VTA-NAc. Despite these molecular changes, food-restricted rats did not display increased reward-seeking behavior. To determine whether metabolic state influences the expression of these neuroadaptations, animals were refed following food-restriction. Refeeding significantly increased nose-poke activity at 24 h through 72 h and subsequently normalized by 168 h. Similarly, reward-seeking behavior was observed following systemic glucose administration in food-restricted rats. Notably, D1R expression followed a temporal pattern similar to behavioral sensitization. D1R expression positively correlated with the increased nose-poke activity observed in refed animals at 24 h and 72 h. In addition, D1R receptor antagonist, SCH23390, significantly reduced reward-seeking behavior in food-restricted rats demonstrating a functional role for D1R signalling in reward sensitization. Food restriction increased MLL1-binding and

H3K4me2 levels at the D1R promoter in the nucleus accumbens, with reciprocal decrease in G9a-binding and H3K9me2 levels. The metabolic state-dependent changes in histone methylation at D1R promoter seemed to underlie reward sensitization. The notion is supported by the observation that the MLL1 knockdown reduced D1R expression, affected histone methylation, and significantly attenuated reward-seeking behavior. In sum, these findings demonstrate a causal role for MLL1- and G9a-mediated histone methylation at the D1R promoter in metabolic state-driven neuroadaptations within the nucleus accumbens that underlie reward sensitization. These results identify an epigenetic mechanism through which metabolic experiences shape future reward responsiveness.

Disclosures: V.A. Borade: None. **D.S. Londhe:** None. **A.J. Sakharkar:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.02/HH28

Topic: H.02. Reward and Appetitive Learning and Memory

Support: PAPIIT-DGAPA IN203124

Title: $GABA_AR$ participation in taste memory and MRI brain changes after long-term sugar consumption

Authors: L. F. BAEZ-REYES, S. I. AGUILAR-GUTIERREZ, E. A. GARZA-VILLARREAL, *M.-I. MIRANDA;
Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: The ability to form associations between a taste stimulus and its consequences promotes individual survival. The insular cortex (IC) is a crucial brain structure for flavor memory, as it integrates information from taste experiences through multiple neurotransmitter systems. In particular, γ-aminobutyric acid $(GABA)_A$ receptors ($GABA_ARs$) have been shown to play a decisive role, since their activation in the IC with muscimol disrupts appetitive saccharin learning, an effect not observed with the $GABA_AR$ antagonist bicuculline. Conversely, bicuculline, but not muscimol, blocks appetitive memory retrieval. In aversion learning, both ligands mitigate conditioned taste aversion (CTA) to saccharin, whereas only muscimol reduces its retrieval. Recent evidence suggests that hedonic value and caloric content influence learning differentially; thus, neurochemical mechanisms might differ between sweeteners, e.g., saccharin vs. sugar. This hypothesis is supported by evidence that rodents prefer sugar over saccharin and elicits stronger latent inhibition of CTA (LI-CTA). Consequently, in this work, $GABA_A$ activity in the IC was evaluated during CTA for sugar and during LI-CTA after long-term sugar exposure. Bilateral IC muscimol injections before CTA acquisition, as well as after 20 days of sugar exposure and before CTA, were performed in male adult rats. Additionally, to evaluate whole-brain neural correlates of LI, rats highly familiarized with sugar underwent magnetic

resonance imaging (MRI) to assess volume or functional changes. The results demonstrate that CTA acquisition is not affected by the muscimol agonist but is significantly delayed in aversive memory extinction. However, the same agonist, after long-term sugar consumption and before CTA, significantly suppressed the expression of appetitive sugar memory, thereby reducing sugar consumption. Surprisingly, despite this decrease in appetitive response, the LI-CTA phenomenon remains intact, as rats showed lower aversive conditioning. These results indicate that IC-$GABA_AR$ operate differentially during taste memory, depending on the degree of sugar familiarity and demonstrates its important modulatory role during high hedonic and familiar memory retrieval. Furthermore, deformation-based morphometry analysis showed regional changes following long-term sugar consumption. Globally, these results shed light on GABAergic participation in sugar taste memory and provide a putative MRI correlate after sugar overconsumption.

Disclosures: L.F. Baez-Reyes: None. **S.I. Aguilar-Gutierrez:** None. **E.A. Garza-Villarreal:** None. **M. Miranda:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.03/HH29

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant 5K01DK134804-03

Title: Individual differences in operant sucrose seeking are associated with distinct temporal patterns of nucleus accumbens dopamine signaling

Authors: *L.-C. CHAO[1], B. A. MATIKAINEN-ANKNEY[2], K. ARBUCKLE[3];
[1]Rutgers University–New Brunswick, Piscataway, NJ; [2]Psychology, Rutgers Univ. Behavioral and Systems Neurosci., Highland Park, NJ; [3]Rutgers, Piscataway, NJ

Abstract: Mesolimbic dopamine signaling in the nucleus accumbens (NAc) plays a critical role in reward seeking and motivated action. Prior studies have shown that NAc dopamine activity is associated with task engagement and action initiation, but less is known about how endogenous dopamine dynamics vary across individuals with different operant response phenotypes. We hypothesized that natural differences in operant responding would be associated with distinct temporal patterns of NAc dopamine activity during reward seeking.To test this, we recorded NAc dopamine activity using fiber photometry following unilateral expression of the genetically encoded dopamine sensor GRABDA (pAAV-hSyn-GRAB-rDA3m) in male and female C57BL/6J mice. Mice were trained in a home-cage fixed-ratio 1 (FR1) task in which a correct left nose poke was reinforced with a 20-mg sucrose pellet. Following acquisition, mice performed the FR1 task in a behavioral chamber while dopamine activity was recorded. Animals were classified into low- and high-responder groups based on total left-poke count.Peri-event

analyses revealed that high-responder mice exhibited earlier dopamine recruitment surrounding correct response events, with dopamine activity rising before or near the operant response. In contrast, low-responder mice displayed a delayed and more prolonged dopamine response following the response event. These preliminary findings suggest that individual differences in operant food seeking are associated not only with dopamine response magnitude, but also with the temporal organization of accumbal dopamine signaling. Together, these results support a model in which NAc dopamine reflects dynamic engagement with reward-seeking actions and evolves with behavioral response phenotype.

Disclosures: L. Chao: None. **B.A. Matikainen-Ankney:** None. **K. Arbuckle:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.04/HH30

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Ekam Imaging

Title: Semaglutide Alters Reward Circuit Activation and Connectivity with Partial but Incomplete Normalization After Washout

Authors: *T. CHUKWUEMEKA[1], B. AXE[1], S. GALLO[1], T. MUSKU[1], R. J. ORTIZ[4], A. MAHESWARI[1], N. CAVALLARO[1], P. P. KULKARNI[2], C. F. FERRIS[3];
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Abstract: Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for type 2 diabetes and body weightmanagement, yet the neural mechanisms underlying their effects on reward processing, appetiteregulation, and metabolism remain poorly understood. Using multimodal Magnetic Resonance Imaging(MRI) in fully awake female Sprague-Dawley rats, we characterized structural, connectivity, andfunctional changes induced by 14-day semaglutide treatment and a 14-day drug-free washout. Rats weredivided into semaglutide (n=9) and vehicle (n=9) groups receiving daily intraperitoneal injections. Doseswere titrated from 5 to 50 μg/kg over 10 days and maintained through day 14. Imaging on a 7T BrukerBioSpec 70/20 USR included T2-weighted anatomical MRI, Blood Oxygen Level Dependent (BOLD)fMRI, and resting state functional connectivity (rsFC), with 0.1 mL of 30% sucrose delivered via bite barduring BOLD acquisitions. Semaglutide reduced body weight and increased volumes in the hippocampus,olfactory system, and sensorimotor cortex. rsFC revealed whole-brain hypoconnectivity across the basalganglia, amygdala, hippocampus, and sensorimotor cortex. Gustatory stimulation elicited suppressedBOLD responses brain-wide, with attenuation in the olfactory system, hippocampus, reward circuitry, andcerebellum. After washout, body weight and differences in stimulus-based BOLD responses recovered.Dopaminergic connectivity

partially renormalized, but network metrics remained below vehicle levels. Atreatment×time interaction for negative BOLD in reward circuitry persisted, indicating incompleterestoration of inhibitory reward processing. Persistent dopaminergic hypoconnectivity after washoutprovides a neurobiological explanation for weight regain following GLP-1 agonist cessation, suggestingthe brain's hedonic set point does not fully reset upon withdrawal. This raises questions about optimaltreatment duration, discontinuation risks, and maintenance dosing. The capacity of semaglutide to inducelasting mesolimbic reorganization after clearance underscores the need for longitudinal neuroimaging inhuman populations to guide evidence-based prescribing for this rapidly expanding drug class.

Disclosures: T. Chukwuemeka: None. **B. Axe:** None. **S. Gallo:** None. **T. Musku:** None. **R.J. Ortiz:** None. **A. maheswari:** None. **N. Cavallaro:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Imaging.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: NRF Grant RS-2025-00554882
IBS Grant IBS-R015-D2
RS-2026-25507282

Title: Internal state modulates dopaminergic responses to oral capsaicin in mice

Authors: *S. KIM[1,4], S. LEE[1,4], G. IM[4,2], S. CHOI[4,2], S.-G. KIM[5,2,3], H. R. KIM[4,1,2,3], C.-W. WOO[4,1,2,3];
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Abstract: Stimulus value is flexibly shaped by an animal’s current physiological needs. Previous studies have shown that internal states such as hunger and thirst modulate reward-related processing and dopaminergic signaling, particularly in response to appetitive stimuli. However, it remains unclear whether internal state can similarly reshape dopaminergic responses to inherently aversive stimuli, such as oral nociceptive inputs. Here, we examined whether thirst state modulates dopamine responses to orally delivered capsaicin in mice. We measured ventral striatal dopamine activity using fiber photometry while delivering 0.04% capsaicin through a

fixed-port forced-delivery procedure (N = 6 mice). We first manipulated thirst state across five days by varying daily water supplementation to establish graded levels of physiological need. Capsaicin-evoked dopamine responses shifted progressively from excitation under heightened thirst to inhibition as thirst was reduced by increased water supplementation. In a separate single-day experiment, we manipulated thirst bidirectionally, first reducing thirst through repeated water consumption and then increasing it by intraperitoneal NaCl injection. Capsaicin-evoked dopamine responses decreased across three successive runs as thirst was reduced, then shifted back toward excitation following thirst reinstatement by NaCl injection, indicating that thirst state bidirectionally and reversibly modulates capsaicin-evoked dopamine responses. These results suggest that the value of an aversive oral nociceptive stimulus is not fixed, but dynamically shaped by the animal's homeostatic need. Although ventral striatal dopamine captures an important aspect of state-dependent capsaicin responses, this modulation may extend beyond dopamine terminals in the ventral striatum. To address this, we established an awake event-related fMRI platform for oral stimulus delivery in mice and are currently validating this platform using water, sucrose, and capsaicin. This approach will allow us to determine how thirst state reshapes whole-brain responses to capsaicin, with water and sucrose serving as non-nociceptive and appetitive comparisons. Together, our findings show that thirst state can shift dopaminergic responses to an aversive oral nociceptive stimulus between excitation and inhibition, motivating ongoing whole-brain experiments on state-dependent stimulus valuation.

Disclosures: S. Kim: None. **S. Lee:** None. **G. Im:** None. **S. Choi:** None. **S. Kim:** None. **H.R. Kim:** None. **C. Woo:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.06/HH32

Topic: H.02. Reward and Appetitive Learning and Memory

Support: KA2024-144010
NIH AA028579
NIH GM162859

Title: Characterizing the effects of citric acid water on mouse health and motivation in addition to performance in virtual reality locomotion-based tasks

Authors: B. MANUEL[1], *G. O. SIPE[2];
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Abstract: Traditionally, complex behavioral tasks in mice have relied upon water restriction as an external motivator to increase task engagement. However, citric acid (CA) water, the technique whereby home cage water is made sour by the addition of small amounts of CA, has

emerged as an alternative to water restriction. Increasing evidence suggests it effectively motivates task performance while improving animal welfare and reducing experimenter labor. While promising, the applicability of CA water in mice remains incompletely characterized with only higher percentages (i.e., 4% and 5%) tested in rats and "ramping" schedules, where CA concentration is successively increased, indirectly examined. Here, we evaluate four CA concentration/schedule combinations (2% nonramp, 4% nonramp, 1-4% fast ramp, and 1-4% slow ramp) for their effects on mouse health (weight change, home cage behaviors, fecal counts) and motivation to drink water (lick counts and drinking behaviors) in female and male C57BL/6J mice. We find that a schedule ramping from 1% to 2% CA after one week is the easiest for mice to adapt to, and that sustained 2% CA use maintains robust lick counts for at least 5 weeks. Additionally, CA has been directly assessed as a motivator for wheel-turning and touchscreen tasks, but not virtual reality (VR) tasks, an increasingly popular class of behavioral experiments in mice. Therefore, we also assess how 2% CA affects motivation and task performance in two VR tasks (running task and stopping task) compared to water controls in female and male C57BL/6J mice. We find that CA water does not increase task performance but does limit competing motivations and produce more uniform, reward-motivated behavior.

Disclosures: B. Manuel: None. **G.O. Sipe:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.07/II1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01MH132019

Title: Selective dopamine D5 receptor activation reduces body weight% in diet-induced obese mice

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Abstract: Obesity remains a major health challenge, and neural mechanisms regulating body weight and feeding behavior remain incompletely understood. Dopamine signaling is implicated in reward-related behaviors, but the contribution of the dopamine D5 receptor to body weight regulation has not been well characterized. To evaluate the effects of D5 receptor activation on body weight, diet-induced obese (DIO) male C57BL/6 mice (n=10/group) were treated with the selective D5 receptor agonist LI-2859 and compared with glucagon-like peptide-1 (GLP-1) receptor agonists as positive control. In a study conducted by a third-party vendor, mice maintained on a 45% high-fat diet received vehicle, LI-2859 (50 or 75 mg/kg, p.o., b.i.d.), or tirzepatide (s.c., every 3 days) for 28 days. In a separate in-house study, mice maintained on a

60% high-fat received vehicle, LI-2859 (50 or 75 mg/kg, p.o., b.i.d.), or semaglutide (s.c., b.i.d.) for 21 days. Body weight changes were analyzed by two-way ANOVA. LI-2859 significantly reduced body weight relative to vehicle controls at the 75mg/kg dose, producing mean body weight changes of -2.44 ± 1.44%. Although semaglutide and tirzepatide produced greater reductions in body weight than LI-2859, the effects of LI-2859 prompted in-house evaluation of the mixed D1/D5 receptor agonist Tavapadon (0.3 or 1 mg/kg, p.o., b.i.d.) using the same mice and treatment paradigm. Tavapadon produced dose-dependent reductions in body weight, with the 0.3mg/kg and 1 mg/kg dose producing mean body weight changes of -6.72 ± 1.30% and of -10.85 ± 0.92% , respectively. The 1mg/kg dose yielded weight loss comparable to that observed with semaglutide. These findings demonstrate that selective D5 receptor activation reduces body weight in DIO mice and suggest that concurrent D5 and D1 receptor activation enhance this effect. Selective D5 receptor activation, though producing significant reductions in weight, does not produce equivalent effects when compared to GLP-1 or GLP-1/GIP agonists while. These findings replicate previous studies showing anorectic effects of D1-like receptor agonists and suggest a specific role for selective D5 activation in DIO models.

Disclosures: M. Masi: None. **G.V. Carr:** Other; G. V. Carr: Scientific advisor to and own stock options in LongTermGevity, Inc..

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.08/II2

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R00DA053388
T32GM148379

Title: Lateral hypothalamus neural activity distinguishes between homeostatic and hedonic feeding.

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Abstract: Obesity, defined by the excessive accumulation of fat, has emerged as a global health crisis, now affecting over 40% of American adults. While lifestyle intervention remains the recommended treatment, the neurobiological reasons of why patients have difficulty to maintain these interventions remain poorly understood. The lateral hypothalamus (LH) is a brain region known for its role in reward-seeking and as a feeding center, yet whether the LH can encode between eating driven by hunger (homeostatic feeding) versus eating driven by pleasure (hedonic feeding) remains an open question. Here, we used cellular-resolution calcium imaging to record LH population activity in freely moving mice during a food-restricted choice feeding task, in which animals could consume either chow or a sugar pellet dispensed at random intervals. We

found that chow bouts and sugar pellet bouts are encoded by distinct LH neuronal populations. Fitting the neural data to a low-dimensional neural manifold revealed that sugar pellet bouts and chow bouts occupy separate, non-overlapping regions of neural state space. Population activity dynamics could also be used to reliably decode between the two bout types. These results indicate that palatable food and chow intake engage fundamentally different population states which also suggest that homeostatic and hedonic may also operate through distinct neural mechanisms. To test this hypothesis, animals underwent the choice feeding task in either a fed or fasted state. Consistent with the results from the earlier experiment, we identified LH neuronal populations with selective activity for palatable food in fed (hedonic) versus fasted states (homeostatic), suggesting the LH may encode these two feeding types through different population states. Together, these findings demonstrate that the LH contains functionally distinct populations that separately represent homeostatic and hedonic feeding, advancing our understanding of how the brain regulates reward-driven overeating and laying the groundwork for therapeutic strategies that target compulsive eating while preserving healthy hunger-driven feeding.

Disclosures: J. Min: None. **G. Park:** None. **C. Xiao:** None. **D. Sarno:** None. **E.H. Nieh:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.09/II3

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Binge-like eating modulation by administration of dopamine D4 antagonist with CB2 receptor agonist in nucleus accumbens

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Abstract: The Endocannabinoid System (ECS) has been identified as a critical modulator of food intake. Also, Binge Eating Disorder (BED), is characterized by uncontrollable episodes of eating in a short period of time, with a subjective loss of control and overconsumption behavior. In this regard, palatable food continuous access induced obesity-like traits with selective ECS changes, whereas intermittent access triggered binge-like behavior accompanied by broader ECS dysregulations. This suggests that CB2 receptor signaling serves as a counter-regulatory mechanism that can dampen hedonic feeding by reducing dopaminergic activity in reward circuits. The shell region of the NAc (NAcSh) participates in adaptive behaviors and reward detection and has been associated with hedonic response to changes in liking. The present study aims to analyze the administration in shell region of the nucleus accumbens of D4R antagonist (L-745870) with CB2R agonist (HU308) or antagonist (AM630), on binge-like intake of PF in male adult rats. Forty male adult Sprague-Dawley rats were used; animals were individually

housed and had ad libitum access to water and standard diet (SD). Animals were evaluated in binge-like intake, with 1h access to palatable food (PF) for twelve binge-like eating (BLE) sessions. Rats were randomly assigned to the following treatment groups and received intra-NacSh microinjections of treatment: 1) vehicle; 2) HU-308; 3) AM630; 4) L-745870, 5) L-745870-HU308 evaluating the effect of these treatments for three additionally BLE sessions. Our results indicate that L-745,870- HU308 reduced binge-like intake of PF, suggesting an interaction between D4R with CB2R to modulate PF intake.

Disclosures: L. Rodriguez-Serrano: None. **M. Chavez Hernandez:** None.

Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.10/II4

Topic: H.02. Reward and Appetitive Learning and Memory

Support: DA060221

Title: Hidden Markov modeling recovers the behavioral context of operant lever pressing during sucrose self-administration

Authors: *D. A. FREEMON[1], A. SANDOVAL, Jr[2], J. SANDOVAL[3], Y. MARMOL CONTRERAS[6], A. THOMAS[4], T. A. GREEN[5];
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Abstract: Operant self-administration is commonly summarized by discrete events: which lever was pressed, how often, how quickly, and how many rewards were earned. These measures quantify responses but provide little information about the behavior surrounding each press. Using deep-learning pose estimation with directional segmentation and hidden Markov modeling, we asked whether peri-event behavioral structure could be recovered from videos of sucrose self-administration. Here, pose refers to video-based estimates of body position and movement. Directional segmentation classifies movement around the lever as approach, withdrawal, or neutral. Male Long-Evans and Sprague-Dawley rats self-administered sucrose on a fixed-ratio 1 schedule. All rats acquired the task and responded in accordance with the reward contingencies. These standard measures established task behavior but still described each press as an event rather than a movement. Pose tracking revealed consistent structure around active lever presses. A directional segmentation model recovered a reliable approach-and-retreat pattern across all 6 rats and 34 sessions, with movement toward the active lever before pressing and away afterward. Within this trajectory, a hidden Markov model built from 13 pose features identified recurring postural states, including an engagement state enriched around active lever

presses whose occupancy increased from 34% before a press to 62% at the press itself. These states also separated active from inactive lever contacts. Active contacts occupied the engagement state 59 percentage points more often than inactive contacts and a disengaged state 51 points less. Thus, active and inactive contacts differed not only by which lever was pressed but by pose-defined state at contact. Operant lever pressing is not a context-free event; it is a sampled moment within a reproducible lever-directed behavioral sequence. Pose-derived state modeling restores that missing behavioral context to the operant record.

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Poster

PSTR071: Feeding, Metabolism, and Natural Reward

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR071.11/II5

Topic: H.02. Reward and Appetitive Learning and Memory

Support: State of Washington

Title: Flavor paired with environmental enrichment is preferred and worked for by rats

Authors: *J. W. GRIMM, A. O'SHEA, A. VON HAGEL, A. CORTEZ-TINAJERO, F. PEDERSEN, J. MURREY, R. BARCOTT, R. HANNAH, S. HOHNDEL;
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Abstract: For rodents, environmental enrichment (EE) reduces interest in highly palatable foods and drugs of abuse. In the present study, we conducted experiments to determine if EE itself is reinforcing. The EE experience was paired with a flavor provided in drinking water. Subjects were adult Long-Evans rats. Experiment 1. Initial flavor preference. Rats were provided with a series of daily choices (plain vs. flavored water, one flavor vs. the other flavor). Rats equally preferred 1% vanilla to 1% almond flavored drinking water. There were no sex differences in preference. There was no preference for flavored water vs. unflavored water. Experiment 2. Flavor paired with Control or EE housing: water bottle choice. Vanilla or almond flavor was paired with 24h EE or Control housing (within and between subject counterbalanced). This was followed by two 1-h choice trials separated by one day. Rats preferred water with flavor that was previously paired with EE. The effect was more robust with male rats. Experiment 3. Flavor paired with Control or EE housing: operant water self-administration. Water restricted (1-h access per day to water) rats first learned to respond for water in operant conditioning chambers (2h/day for 10 days). Vanilla flavor was paired with 24h EE or Control housing (between groups counterbalanced). This was subsequently followed by a return to operant-based responding for the flavor/no flavor that was previously paired with EE or Control housing. Rats with a history of Control housing responded for more liquid overall vs. rats with a history of EE housing. Rats with a Control housing history responded less for the flavored vs. unflavored water paired with

Control housing. In contrast, rats with a history of EE housing responded more for the flavored water vs. unflavored water paired with a history of EE housing. The effect was more robust with male rats. Summary: Rats drank or worked for more presentations of water that contained a previously neutral flavor paired with EE. The effects were more pronounced in male rats. The results of Experiments 2 and 3 support the hypothesis that EE is reinforcing.

Disclosures: J.W. Grimm: None. **A. O'Shea:** None. **A. von Hagel:** None. **A. Cortez-Tinajero:** None. **F. Pedersen:** None. **J. Murrey:** None. **R. Barcott:** None. **R. Hannah:** None. **S. Hohndel:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.01/II6

Topic: H.04. Emotion

Title: Delayed anxiogenic effects of acute immobilization stress depend on sex

Authors: *C. J. GOTTRON, N. M. MOLNAR, E. J. SCHNEIDER, J. T. PARKER, S. M. REGAN, S. M. LAMBDIN, K. M. KING, M. J. SAVINI, S. E. STRAUB, T. R. WELKER, K. E. WILLIAMS, A. M. BACH, P. R. ZOLADZ;
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Abstract: Symptoms of post-traumatic stress disorder (PTSD) do not always begin immediately following stress exposure. Instead, these symptoms can manifest after an incubation period, during which PTSD-related sequelae progressively develop over time. Understanding the delayed effects of acute stress is critical, as it could generate improved interventions to prevent or reverse PTSD-related symptomatology. Preclinical work has shown that, in male rats, acute immobilization stress induces a delayed increase in anxiety-like behavior and dendritic hypertrophy in the amygdala. Although women exhibit greater vulnerability to PTSD, few studies have investigated whether acute stress can provoke a delayed onset of PTSD-related symptoms in females. This study aimed to fill this gap in the literature. On day one, adult male and female Sprague-Dawley rats were immobilized in plastic DecapiCones for two hours. Rats in the control group remained in their home cages for the duration of the stress procedure. Ten days later, all rats underwent a 5-minute trial on an elevated plus maze (EPM) to assess anxiety-like behavior. The next day, the rats underwent an assessment of their acoustic startle response (ASR), which measures hyperarousal. Immobilized males exhibited greater anxiety-like behavior, as reflected by reduced time spent in the open arms and intersection of the EPM. This effect was not observed in immobilized females. No significant effect of immobilization stress was observed for the ASR in males or females. These findings suggest that the delayed manifestation of PTSD-related symptoms may be sex-dependent. Future studies should examine the neurochemical mechanisms that could underlie such differences.

Disclosures: C.J. Gottron: None. **N.M. Molnar:** None. **E.J. Schneider:** None. **J.T. Parker:** None. **S.M. Regan:** None. **S.M. Lambdin:** None. **K.M. King:** None. **M.J. Savini:** None. **S.E. Straub:** None. **T.R. Welker:** None. **K.E. Williams:** None. **A.M. Bach:** None. **P.R. Zoladz:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.02/II7

Topic: H.04. Emotion

Title: Psilocybin and norbaeocystin exert acute, dose-dependent, anxiogenic effects that depend on sex

Authors: *E. J. SCHNEIDER[1], C. J. GOTTRON[1], N. M. MOLNAR[1], J. T. PARKER[1], S. M. REGAN[1], S. M. LAMBDIN[1], K. M. KING[1], M. J. SAVINI[1], S. E. STRAUB[1], T. R. WELKER[1], K. E. WILLIAMS[1], A. M. BACH[1], A. JONES[2], P. R. ZOLADZ[1];
[1]Psychology & Educ., Ohio Northern Univ., Ada, OH; [2]Chemical, Paper, and Biomed. Engin., Miami Univ., Oxford, OH

Abstract: Single treatments with psychedelics have demonstrated rapid and long-lasting antidepressant effects. However, psychedelics often produce unfavorable psychoactive effects that could worsen existing psychological distress in individuals with depression and anxiety. Thus, there is interest in identifying compounds that are similar to psychedelics but do not produce such adverse side effects. Several psilocybin-related tryptamines that do not produce psychoactive effects can be found in “magic” mushrooms, and previous work has shown that some of them induce antidepressant effects in preclinical models. Less is known about the acute impact of these agents on anxiety-like behavior, and because psychedelics can exert acute anxiogenic effects, it is important to determine whether related compounds do the same. Thus, we compared the dose-dependent effects of psilocybin (PSIL) and norbaeocystin (NOR) on anxiety-like behavior in male and female rats. In the first experiment, Sprague-Dawley rats were treated with PSIL (0.3, 0.6, or 1 mg/kg), NOR (0.3, 0.6, or 1 mg/kg), or vehicle 30 min prior to a 5-min trial on an elevated plus maze. In males, every dose of PSIL and NOR led to reduced time in the open arms. In females, only 1 mg/kg PSIL led to reduced time in the open arms. In the second experiment, rats were administered the same treatments as the first experiment 30 min prior to a 10-min trial in an open field. In males, 1 mg/kg PSIL led to less exploration of the center area and less locomotor activity. The lowest dose of NOR led to greater exploration of the center area, and both 0.3 and 0.6 mg/kg doses led to greater locomotor activity. In females, 1 mg/kg PSIL led to less locomotor activity, while 0.3 and 0.6 mg/kg led to greater locomotor activity. Both 0.3 and 0.6 mg/kg NOR resulted in greater exploration of the center area and greater locomotor activity. Collectively, these results indicate that both PSIL and NOR exert acute anxiogenic effects in males, while only higher doses of PSIL exert such effects in females. Indeed, there was some evidence to suggest that lower doses of NOR exert acute anxiolytic

effects in females. These findings warrant further examination, particularly to determine the neurological mechanisms that may underlie such sex differences.

Disclosures: E.J. Schneider: None. **C.J. Gottron:** None. **N.M. Molnar:** None. **J.T. Parker:** None. **S.M. Regan:** None. **S.M. Lambdin:** None. **K.M. King:** None. **M.J. Savini:** None. **S.E. Straub:** None. **T.R. Welker:** None. **K.E. Williams:** None. **A.M. Bach:** None. **A. Jones:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EYWA Biotech. **P.R. Zoladz:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.03/II8

Topic: H.04. Emotion

Title: Role of estrous in the acute anxiogenic effects of psilocybin and the related tryptamine, norbaeocystin

Authors: *N. M. MOLNAR[1], M. J. SAVINI[1], C. J. GOTTRON[1], E. J. SCHNEIDER[1], J. T. PARKER[1], S. M. REGAN[1], S. M. LAMBDIN[1], K. M. KING[1], S. E. STRAUB[1], T. R. WELKER[1], K. E. WILLIAMS[1], A. M. BACH[1], A. JONES[2], P. R. ZOLADZ[1];
[1]Psychology & Educ., Ohio Northern Univ., Ada, OH; [2]Chemical, Paper, and Biomed. Engin., Miami Univ., Oxford, OH

Abstract: Existing pharmacotherapy for many psychiatric conditions is largely ineffective and is associated with numerous adverse side effects. Thus, researchers have shifted their attention toward identifying novel treatments, such as psychedelics, for these disorders. Relative to males, females are at greater risk of developing stress- and anxiety-related disorders and are more susceptible to the adverse side effects of psychotropic medications. In addition, recent work suggests that psychedelics may exert sex-dependent effects on behavior. Therefore, we examined the impact of PSIL and the related non-psychoactive tryptamine, norbaeocystin (NOR), on anxiety-like behaviors in female rats; we also assessed whether the female estrous cycle would influence any observed effects. Vaginal cells were collected from female Sprague-Dawley rats for a total of 15 days, and the Shorr staining method was used to identify estrous stage in the rats. On Days 11 and 14, the rats were injected with PSIL (0.6 mg/kg), NOR (0.6 mg/kg), or vehicle (0.9% saline) 30 min before being tested on an elevated plus maze (EPM; Day 11) or having their acoustic startle response (Day 14) measured. Rats in estrus spent more time in the open arms of the EPM (i.e., less anxiety) than rats in any other stage. Independent of estrus stage, PSIL-treated rats spent less time in the open arms of the EPM (i.e., greater anxiety) than NOR- or vehicle-treated rats. When rats in estrus were treated with PSIL or NOR, they exhibited greater habituation of their startle responses than vehicle-treated controls. These findings suggest that NOR may be a more promising candidate to treat anxiety-related symptoms in females, as it

does not exert acute anxiogenic effects and can reduce symptoms of hyperarousal when given during specific times of the female hormone cycle.

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Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.04/II9

Topic: H.04. Emotion

Support: Nagoya City University
KAKENH 23K18257

Title: Chronic exposure to aversive stimuli associated with early-life atopic dermatitis-like inflammation alters anxiety-related behavior and locomotor activity in mice

Authors: *M. SHINDO[1], D. MUSTIKA[3], S. TOMINAGA[1], H. HIDA[2];
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Abstract: The postnatal developmental period is a critical window for the formation of neural circuits underlying emotion-related behavior. Persistent aversive somatosensory input, such as chronic itch, during this period may have long-term effects on emotion-related behavior. Consistent with this idea, atopic dermatitis (AD), a chronic inflammatory skin disease characterized by severe itch, has been associated with neuropsychiatric symptoms, including attention-deficit/hyperactivity and anxiety. However, it remains unclear how persistent chronic itch during early life affects subsequent emotion-related behavior.
To address this question, we established an early-life atopic dermatitis-like mouse model by repeated topical DNFB application for 5 weeks beginning in the early post-weaning period. Subsequently, locomotor activity and anxiety-related behavior were examined in adulthood. During development, DNFB-treated mice exhibited skin inflammation and scratching behavior. In the open field test, DNFB-treated mice showed a significant increase in total distance traveled, indicating increased locomotor activity. In the elevated plus maze test, DNFB-treated mice tended to spend less time in the open arms, suggesting possible changes in anxiety-related behavior.
These findings suggest that aversive somatosensory input associated with early-life AD-like inflammation may induce long-lasting changes in locomotor activity and anxiety-related

behavior, potentially affecting the maturation of emotion-related neural circuits through skin-brain interactions. We are currently investigating neural activity marker expression in brain regions involved in itch transmission and emotional regulation, including the amygdala, parabrachial nucleus, and prefrontal cortex. We are also examining the relationships among skin inflammation severity, scratching behavior, adult behavioral phenotypes, and neural activity changes.

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Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.05/II10

Topic: H.04. Emotion

Support: FIG Grant IITR/SRIC/2741

Title: Self and other-directed threat processing: A virtual reality experiment

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Abstract: The selection of human defense responses is influenced by contextual factors such as whether the threat is directed towards oneself or another. Research on predatory imminence continuum has examined the threat responses directed to the organism. However, less is known if the same responses (fight-or-flight) differ similarly when threat is directed to another conspecific. The present ongoing study investigates fight-or-flight defense responses in self-directed and other-directed threat conditions. Eighteen participants were divided into self-directed (SeD) (N=9, Mean(SD)=24(3.71)) and other-directed (OtD) (N=9, Mean(SD)=22.22(3.15)) groups. In the SeD group, participants were presented with a virtual reality (VR) scenario, with 4 lanes and were assigned to search for a box. During the search they might encounter a threat avatar running towards them, at distal and proximal locations. The conditions were: Distal Threat Escape, Distal Threat No Escape, Proximal Threat Escape, Proximal Threat No Escape and No Threat. In the OtD group, the threat was directed towards another neutral avatar. In both VR scenarios, participants responded with Fight-or-Flight responses towards the threat. In both the groups, a total of 20 trials (4x5 conditions) were included. A condition (4) x group (2) mixed ANOVA was conducted for Fight and Flight responses. It revealed a significant main effect of Conditions for Fight ($F(3,48) = 5.34$, $p<0.01$, $\eta p^2=0.25$). and Flight responses ($F(3,48) = 5.34$, $p<0.01$, $\eta p^2=0.25$). This indicated that the proportion of fight-or-flight responses varied across conditions. For eye tracking data, dwell time on Environment, Threat and Neutral avatar regions of interest (ROI) was calculated. For SeD group, a Conditions (4) x ROI (2) mixed ANOVA revealed a significant main effect for ROI

($F(1,6)=45.79$, $p<0.01$, $\eta p^2=0.88$). For OtD group, a Conditions (4) x ROI (3) mixed ANOVA revealed a significant main effect for ROI ($F(2,16)=304.42$, $p<0.01$, $\eta p^2=0.97$) and Conditions ($F(3,24)=27.18$, $p<0.01$, $\eta p^2=0.77$). This suggests that the participants allocated attention differently across ROIs. A significant Conditions x ROI interaction effect was also observed ($F(6,48)=10.55$, $p<0.01$, $\eta p^2=0.57$). This indicated that the pattern of the visual attention towards the ROI varied across conditions. The current research may contribute to the threat processing literature in simulation-based VR increasing the ecological validity of the paradigm. It provides evidence that defensive reactions are influenced by context and evaluation of dynamic environmental information before selecting a response strategy.

Disclosures: V. Maithani: None. **M.K. Asthana:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.06/II11

Topic: H.04. Emotion

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We also thank Consejo Quintanarroense de Humanidades Ciencia y Tecnología (COQCHYT) for the scholarship given to N.V-A within the Program for the Critical Thinking Strengthening of Quintana Roo goverment.

Title: Sex differences in anxiety- and depression-like behaviors in an animal model of type 2 diabetes

Authors: *D. REBOLLEDO-SOLLEIRO[1], N. VELASCO-ARAGON[2], O. R. HERNANDEZ PEREZ[3], A. FERNÁNDEZ-GUASTI[4];
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Abstract: Anxiety and depression are highly prevalent mental disorders and leading causes of disability worldwide, with increased prevalence in type 2 diabetes mellitus (T2DM) patients. Although marked sex differences are documented, preclinical studies mostly use male rodents administered with streptozotocin (STZ) to induce hyperglycemia. Neonatal STZ administration in rats also provokes impaired glucose tolerance (IGT), a feature of insulin resistance. However, knowledge regarding females and estrous cycle fluctuations remains limited. This study evaluated sex differences in anxiety- and depression-like behaviors in a T2DM rat model (neonatal STZ-treatment) and determined whether female behaviors vary across estrous cycle stages (ECS). Neonatal male and female rats received STZ (70 mg/kg, i.p.) and were considered

diabetic if they exhibited IGT at 8 weeks. Blood glucose, body weight (BW), food intake (FI), and water consumption (WC) were registered. In females, ECS were monitored via vaginal cytology. At 12 weeks, anxiety- and depression-like behaviors were assessed using defensive burying (DBT) and forced swim tests (FST), respectively. Spontaneous locomotor activity (SLA) and motor coordination (MC) were evaluated to rule out motor impairments. Data normality was assessed with the D'Agostino-Pearson test. Three-way repeated-measures and Two-way ANOVAs were performed for metabolic and behavioral data, respectively (significance at $p < 0.05$). Neonatal STZ-treatment induced IGT, and increased WC and FI. Males showed greater BW and FI. In females, the proportion of rats exhibiting estrous decreased. In the DBT, diabetic males displayed increased freezing (passive coping), whereas diabetic females showed increased burying (active coping). In the FST, diabetic rats of both sexes showed increased immobility and reduced swimming, indicating a depression-like profile. No changes in SLA or MC occurred. Female behaviors did not vary by ECS. These results demonstrate that neonatal STZ-treated rats develop T2DM-like metabolic alterations associated with anxiety- and depression-like profiles. Remarkably, anxiety-like behaviors differed between sexes, while depressive-like behaviors were unaffected by sex or ECS, emphasizing the importance of considering sex differences and endocrine variables, thereby improving the interpretation of preclinical findings and contributing to the development of more precise therapeutic strategies.

Disclosures: D. Rebolledo-Solleiro: None. **N. Velasco-Aragon:** None. **O.R. Hernandez Perez:** None. **A. Fernández-Guasti:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.07/II12

Topic: H.04. Emotion

Title: Mapping the Subjective Experience of Threat in Chronic Pain Using Natural Language Processing and Functional Neuroimaging

Authors: *J. CHA[1,4], J.-J. LEE[4], J. HAN[1,4], C.-W. WOO[1,4,2,3];
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Abstract: Chronic pain is a multidimensional and inherently subjective experience that varies considerably across individuals. Given this subjectivity, a central question is how patients' personal experiences are organized and, in particular, what they perceive as threatening. To investigate this, we used a densely sampled precision dataset from a chronic pain patient (N = 1) diagnosed with fibromyalgia. Over 30 longitudinal visits, the participant completed guided interviews narrating personal experiences and provided corresponding continuous threat ratings. Functional Magnetic Resonance Imaging (fMRI) was also acquired during interview listening,

and Acceptance and Commitment Therapy (ACT) was introduced from session 21 onward. To analyze the semantic content of the interviews, we extracted context-sensitive text embeddings using a Large Language Model (LLM) to map the subjective nuances of the narrative into a high-dimensional semantic space. A Partial Least Squares Regression (PLS-R) model trained on these contextualized embeddings successfully predicted the continuous threat ratings ($r = 0.41$, $p < .001$). To interpret which clinical dimensions the model associated with threat, we projected clinical survey items onto the PLS-R weights. Two dimensions - impairment of daily functioning and the inability to live by one's personal values - aligned significantly more strongly with the threat-predictive weights than the pain dimension (Mann-Whitney U test; functional impairment vs. pain: $U = 187$, FDR-corrected $p < .001$; valued living vs. pain: $U = 119$, FDR-corrected $p = .009$). Furthermore, a semantic distance analysis demonstrated this pattern at the narrative level, with stronger alignment to functional impairment and the failure to live by personal values than to pain (Steiger's z; functional impairment vs. pain: $z = 6.63$, $p < .001$; valued living vs. pain: $z = 7.06$, $p < .001$). This threat-to-life-disruption semantic coupling significantly decreased following ACT administration (Fisher's r-to-z; functional impairment: $z = -2.01$, $p = .045$; valued living: $z = -3.94$, $p < .001$). Together with neural correlates of threat processing observed in the fMRI data, these findings suggest that threat in chronic pain is organized less around pain itself and more around the disruption it imposes on daily functioning and valued living.

Disclosures: J. Cha: None. **J. Lee:** None. **J. Han:** None. **C. Woo:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.08/II13

Topic: H.04. Emotion

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Title: Effect of patterned transcranial magnetic stimulations of the prefrontal cortex in modulating anxiety

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Abstract: Anxiety disorders are highly prevalent and recurrent, substantially impairing daily functioning, while pharmacotherapy is limited by long-term side effects and the development of tolerance. Although Transcranial magnetic stimulation (TMS) is gaining attention as a noninvasive therapeutic alternative, preclinical evidence remains insufficient regarding how

TMS patterning modulates anxiety and fear behaviors when delivered to the same target. Here, we evaluated whether patterned TMS protocols targeting the mouse frontal association cortex (FrA; bregma AP +3.2, ML −0.75) differentially modulate anxiety and fear behaviors. To compare pattern-dependent TMS effects, effects of thalamic burst TMS, continuous theta-burst stimulation (cTBS), or tonic TMS protocols on anxiety and fear-related behaviors were examined. F1 hybrid male mice (C57BL/6J × 129/SvJae) were randomly assigned to sham or TMS groups. To assess anxiety-related exploratory behavior, mice received repeated TMS to the FrA via a small coil mounted on the skull prior to the open field test (OFT) and Elevated plus maze (EPM). Mice underwent object-paired fear conditioning (0.55 mA, 10 shocks) to establish a fear memory, followed by cumulative TMS applied for 3 days (10 min/day) before the behavioral assays. Defensive burying behavior was then quantified on days 7, 14, 21, and 28 over a 4-week period. Thalamic burst TMS induced significant anxiolytic-like behavioral changes, including increased center exploration in the OFT and increased open-arm exploration in the EPM. Similarly, in the underwent object-paired fear conditioning test, thalamic burst TMS exhibited a significantly greater fear-reducing effect compared to cTBS or tonic TMS. While all active TMS protocols mitigated defensive responding compared to the sham group, the thalamic burst pattern was the most effective, significantly attenuating fear-induced defensive behaviors and uniquely promoting proactive interaction with the fear-conditioned object. Together, these findings indicate that while prefrontal TMS generally mitigates fear, the thalamic burst pattern exerts a superior effect, supporting that different TMS patterns have differential effects, and therefore, emphasizing the importance of optimizing prefrontal TMS protocols.

Disclosures: H. Kim: None. **S. Park:** None. **Y. Huh:** None. **J. Cho:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.09/II14

Topic: H.04. Emotion

Title: Steroid-Independent Modulation of Anxiety-like Behavior in Orchidectomized B6D2F1 Male Mice

Authors: *A. M. WILES[1], J. KIRKER[2], J. PARK[3], E. MICCICHE[2];
[1]Psychology, [2]Univ. of Massachusetts Boston, Boston, MA; [3]Psychology, Univ. of Massachusetts, Boston, Boston, MA

Abstract: In many mammalian species, gonadal steroids, particularly testosterone, play a critical role in modulating numerous social behaviors, including both reproductive activity and emotional regulation. Testosterone is widely believed to be necessary and sufficient to activate male sexual behavior and is known to exert anxiolytic effects. However, some individuals maintain sexual behavior and emotional resilience despite the absence of circulating androgens, suggesting the existence of gonadal steroid-independent mechanisms. The pathways that

maintain motivated behavior and emotional resilience in hypogonadal conditions remain poorly understood.
The B6D2F1 hybrid mouse provides a unique model for investigating these mechanisms, as one-third of these males continue to display sexual behavior long after castration (herein referred to as “maters”). Preliminary results from our lab indicate that maters, relative to their non-mater counterparts, display significantly reduced anxiety-like behaviors in both the Open Field Test and Elevated Plus Maze. The co-occurrence of persistent male sexual behavior and attenuated anxiety-like behaviors in maters suggests that similar steroid-independent mechanisms may be driving resilience across both motivational and affective domains.
To validate our pilot data, we conducted a larger-scale study incorporating the previous behavioral assays alongside physiological measurements of serum corticosterone concentrations and gene expression of biological markers associated with anxiety modulation. This research leverages an innovative model to dissect gonadal steroid-independent mechanisms underpinning emotional resilience, offering insights that may inform our understanding of hypogonadal states, affective disorders, and novel avenues of anxiety regulation.

Disclosures: A.M. Wiles: None. **J. Kirker:** None. **J. Park:** None. **E. Micciche:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.10/II15

Topic: H.04. Emotion

Support: CAPES (88887.842546/2023-00, 0001)
CNPq (317032/2023-2)

Title: The role of amygdala oxytocinergic neurotransmission on emotional contagion of chronic pain in male and female mice

Authors: A. SCALLI PEDRO[1,2], R. BRANDÃO-DE-SOUZA[1,3], ***A. CANTO-DE-SOUZA**[4,2,3]; [1]1Psychobiology Group, Dept. of Psychology/CECH-Universidade Federal de São Carlos-UFSCar, São Carlos, Brazil; [2]2Joint Grad. Program in Physiological Sci. UFSCar/UNESP, São Carlos, Brazil; [3]3Program in Psychology UFSCar, São Carlos, São Paulo, Brazil; [4]1Psychobiology Group, Dept. of Psychology, CECH-Universidade Federal de São Carlos-UFSCar, Brazil

Abstract: Previous studies show that oxytocinergic neurotransmission modulates social and affective behaviors, cognition, and pain, with systemic oxytocin (OXT) attenuating hypernociception in cohabiting male and female mice subjected to chronic pain. Additionally, the amygdala (AMY) is involved in nociceptive and emotional responses, modulating the emotional contagion of chronic pain in rodents. This study investigated the role of oxytocinergic neurotransmission in the AMY on the emotional contagion of chronic pain in male and female

mice. Male and female Swiss mice (n=6-8/group) were housed in pairs for 28 days. On day 14, one mouse from each pair was assigned to either cagemate nerve constriction (CNC) by sciatic nerve constriction (SNC) or cagemate sham (C) by sham surgery. The remaining one cagemate became observer CNC (Ob-CNC) or observer sham (Ob-S). On day 24, the Ob-CNC or Ob-S mice were subjected to stereotaxic surgery. On day 28, Ob-CNC and Ob-S mice received a subcutaneous (s.c.) injection of saline or OXT (2.0 mg/kg). Twenty-five minutes later, they received bilateral injection intra-amygdala atosiban (AT, an oxytocin receptor antagonist, OXTR), 0.4 µg/0,1 microliters) or saline. After intra-amygdala injections, mice received acetic acid (0.6%, 0.1 ml/10g i.p.) and were submitted to the writhing test. The hot plate test revealed that the SNC procedure increased pain response in male ($t_{(52)}$= 2.06, $p < 0.05$) and female ($t_{(51)}$= 2.85, $p < 0.05$) CNC cagemates. Three-way ANOVA revealed significant effects for interaction effects for cohabitation x pre-treatment x treatment for systemic injections for males [$F_{(1,46)}$= 9.89, $p<0.05$] and females [$F_{(1,45)}$= 5.56, $p<0.05$]. The Duncan test revealed that OCT (s.c.) and intra-amygdala saline decreased the number of abdominal contortions in male and female Ob-CNC mice ($p<0.05$). Intra-AMY atosiban did not alter hypernociception in Ob-CNC mice compared to the Ob-S ($p>0.05$). These results demonstrate that living in pairs with a mouse subjected to CNC induces hyperalgesia in both male and female Ob-CNC. Systemic OXT produced antinociception in these animals. Intra-AMY AT, a dose devoid of any intrinsic effect on chronic pain, completely blocked the antinociceptive effects of systemic OXT. These findings suggest that oxytocinergic neurotransmission of the amygdaloid complex in modulates the emotional contagion of pain responses in male and female mice.

Disclosures: A. Scalli Pedro: None. **R. Brandão-de-Souza:** None. **A. Canto-de-Souza:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.11/II16

Topic: H.04. Emotion

Support: R15MH140275

Title: Sex-dependent effects of Lactobacillus rhamnosus on anxiety-like behavior and corticosterone response

Authors: *C. E. HARTSGROVE[1,2], G.-M. WALKER[1], K. D. SILVA[1], K. NUNEZ[1], K. ALEJOS[1], M. JOSEPH[1], K. HARRIS[1], J. LIN[3], K. CADET[1], R. MANIANI[1], A. S. TRAN[1], L. Y. MAENG[1,2];
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Abstract: The gut-brain axis has been implicated in fear-related psychiatric disorders including anxiety and post-traumatic stress disorder (PTSD) - which are characterized by impaired fear

extinction, the learned inhibition of fear after a threat is no longer present. There is increasing evidence that gut microbiome manipulations can impact stress and anxiety in rodent models. The probiotic Lactobacillus rhamnosus (L. rhamnosus) has been shown to reduce anxiety-like behavior in animal models, but LR effects on fear and hormonal stress responses have only been studied in males, despite sex differences in fear extinction. Whether the anxiolytic effects of L. rhamnosus are sex-dependent is still unclear. We investigated sex differences in the effects of L. rhamnosus on anxiety-like behaviors, fear extinction, and hormonal stress responses. Adult Sprague Dawley rats (n=56) received L. rhamnosus or vehicle (PBS) treatment for 21 days. Anxiety-like behavior was examined using the elevated plus maze (EPM). Serum corticosterone levels (CORT) were quantified before and after the EPM. A 3-day auditory cued fear conditioning/extinction paradigm was used to examine extinction learning and memory. There were no significant effects of sex or L. rhamnosus treatment observed in fear conditioning, fear extinction, or extinction recall [$p>0.05$]. Immunofluorescence was used to quantify inhibitory activity in the fear extinction network during recall by targeting c-Fos and GAD67. A linear mixed effects model revealed an effect of region on GAD67 expression in the medial prefrontal cortex [$F(1,36)=7.410$, $p=.010$], with the infralimbic cortex showing greater GAD67 expression, as well as a trending interaction of sex and group [$F(1,36)=3.647$, $p=.064$]. Sex [$F(1,25.904)=4.626$, $p=.041$] and region [$F(2,25.724)=40.700$, $p<.001$] differences were observed in c-Fos activity in the hippocampus, with females showing greater neural activity in the dentate gyrus compared to males. In the EPM, females had a significantly greater open/closed arm entries ratio [$p=.009$] and duration ratio [$p=.003$], indicating that female rats exhibited less anxiety compared to males. L. rhamnosus administration decreased closed arm duration in the EPM in both males and females [$p=.029$]. Females also exhibited a lower average percent change in serum CORT levels after EPM compared to males [$p=.002$]. Pairwise comparisons revealed that L. rhamnosus-treated females had a lower CORT response than L. rhamnosus-treated males [$p=.003$]. These findings highlight sex differences in anxiety-like behavior and in the effects of probiotic supplementation on neural activity and CORT response to acute stress.

Disclosures: C.E. Hartsgrove: None. **G. Walker:** None. **K.D. Silva:** None. **K. Nunez:** None. **K. Alejos:** None. **M. Joseph:** None. **K. Harris:** None. **J. Lin:** None. **K. Cadet:** None. **R. Maniani:** None. **A.S. Tran:** None. **L.Y. Maeng:** None.

Poster

PSTR072: Fear, Anxiety, Threat, and Pain: Neural Mechanisms of Aversive States

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR072.12/II17

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Fear engrams are formed in the locus coeruleus under contextual fear conditioning in a mouse model

Authors: M. SHIMIZU, ***A. STAVNEZER**;
Neurosci., Col. of Wooster, Wooster, OH

Abstract: Contextual fear memory is a vital survival mechanism that allows organisms to recognize and respond to environments associated with danger. Fear memory is closely linked to posttraumatic stress disorder (PTSD), a psychological condition triggered by traumatic experiences that result in persistent symptoms, such as flashbacks and hypervigilance. Traditional research on fear memory has focused on the hippocampus and amygdala, brain regions responsible for learning and emotional processing, respectively. However, recent studies have drawn attention to the Locus Coeruleus (LC) known for regulating arousal and stress responses through neurotransmitter release. The LC modulates hippocampal and amygdala activation and is an intermediate pathway between the brain and the vagus nerve, indicating a direct connection to the autonomic nervous system.
This study investigated whether the LC directly participates in contextual fear memory storage through the formation of engrams, neuronal populations that encode and retain specific memories, in 14 TRAP2 mice. Using contextual fear conditioning and immunohistochemistry, we found that fear engrams are formed in the LC to store fear memories directly, rather than merely modifying them by indirectly modulating higher regions. Our finding suggests the existence of extinction engrams in the LC that may be suppressing the reactivation of original fear engrams.
The present study opens new potential strategies for treating PTSD by targeting the LC, including neuromodulatory interventions with vagus nerve stimulation to actively “reshape” memory storing networks in combination with current exposure therapy, engram-circuit specific neuromodulation, and pharmacological approaches to LC engrams.

Disclosures: M. Shimizu: None. **A. Stavnezer:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.01/II18

Topic: I.03. Decision Making

Support: NIH Grant MH137210

Title: Planning in a complex board game by non-human primates

Authors: ***E. SHIN**[1], J. LEI[2], M.-Y. PARK[1], B. VAN OPHEUSDEN[3], R. LAUTENSCHLAGER[1], D. MITTLER[1], W. MA[2], D. LEE[1];
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Abstract: Adaptive planning is essential for achieving optimal outcomes in dynamic environments. Previous human studies using the complex board game “Four-in-a-Row” have

shown that planning depth increases with expertise and that deeper planning is impaired following ventromedial prefrontal cortex lesions, suggesting that distinct neural mechanisms may support different levels of planning. However, the neural computations underlying complex planning remain poorly understood. To investigate this, we trained two monkeys to perform a "Four-in-a-Row" task. Each game began with a move by a computer opponent on a 4 × 9 board displayed on a monitor. The monkey then selected an empty position using a joystick-controlled cursor. Players alternated turns until either the monkey or the computer connected four pieces horizontally, vertically, or diagonally. The monkey received a juice reward only when they completed four in a row before the opponent, requiring continuous evaluation of the evolving board state and adaptive adjustment of future choices. To identify the behavioral factors influencing choice, we fit a logistic regression model to the choice behavior of one monkey using multiple board features, including opportunities to create two-, three-, or four-in-a-row configurations and opportunities to block the opponent's three- or four-in-a-row configurations. The monkey significantly considered all connection-related features when making choices, assigning greater weight to longer connections. In addition, a control feature describing the distance from the monkey's previous piece did not significantly explain choice, indicating that behavior was not explained by simple sequential placement strategies. These results demonstrate that non-human primates utilize multiple strategically relevant board features during decision-making in a complex competitive game. Future analyses will characterize planning in monkeys and compare their strategies with those of humans, providing insights into the evolutionary origins of complex planning and informing future investigations of its neural mechanisms in non-human primates.

Disclosures: E. Shin: None. **J. Lei:** None. **M. Park:** None. **B. van Opheusden:** None. **R. Lautenschlager:** None. **D. Mittler:** None. **W. Ma:** None. **D. Lee:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.02/II19

Topic: I.03. Decision Making

Support: NARSAD Young Investigator Grant
NIH/NIDA Grant R00DA055641

Title: The orbitofrontal cortex defines credit assignment in latent learning

Authors: *E. MRUG[1], K. M. COSTA[2];
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Abstract: Animals use cognitive maps, or internal representations of the world, to guide behavior in changing environments. These maps store learned and inferred information about

environmental states and contingencies that can inform future decisions. Cognitive maps have a critical role in latent learning, where information is learned without affecting ongoing task-related behavior. Previously, we showed that lateral orbitofrontal cortex (OFC) is required for accurate credit assignment in non-latent, or explicit, reward-related associative learning. Specifically, OFC inactivation makes learning imprecise, confounding separate contingencies during map creation. However, disruptions to OFC, whether by direct inactivation or in pathological states, like after drug self-administration, also affect latent learning. It is unknown whether credit assignment imprecision can also explain these changes, in part due to the difficulty of modeling latent learning, which is, by definition, behaviorally silent.
To answer this question, we created a computational model capable of modeling latent learning from its later expression. Our model builds on a model-based reinforcement learning framework, but separates latent and explicit learning rates and retrofits parameters from observed data. We tested whether the same imprecision parameter capable of explaining explicit OFC-impaired learning could also explain changes to *latent* learning following targeted OFC inactivation during latent learning or following cocaine self-administration. We also tested different methods of implementing imprecision, particularly in the case of cocaine self-administration, which could affect both latent and explicit learning.
We found that, when compared to alternative models, adding imprecision in latent learning *alone* most parsimoniously explains the effects of both targeted OFC inactivation and cocaine exposure. Within this model, OFC disruption only increased imprecision, with other learning rate parameters unchanged. These results held across a variety of assumptions for animals' prior expectations of reward.
Overall, our results suggest that a partially-imprecise learning system best captures OFC-related deficits in latent learning, indicating that OFC defines precision of encoded associations. Furthermore, we found that the imprecision following cocaine exposure can be localized to latent learning alone. Taken together with our previous results and other published work, these findings suggest that the OFC is particularly important for adding information that is not directly task-relevant into cognitive maps.

Disclosures: E. Mrug: None. **K.M. Costa:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.03/II20

Topic: I.03. Decision Making

Support: IBS-R001-D2

Title: Distributed neural dynamics underlying sensory-to-motor transformation during olfactory decision making

Authors: *J. DO, D. LEE;
Ctr. for Memory and Glioscience, Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Perceptual decision-making requires neural circuits to transform sensory inputs into appropriate actions, yet decision-related activity is often intertwined with stimulus identity, choice, and movement. How these components are distributed across the brain and reorganized through learning remains unclear, particularly in olfactory-guided behavior. Here, we addressed this question using acute and chronic Neuropixels recordings during an olfactory delayed match-to-sample task. Mice compared two sequential odors separated by a delay and indicated whether they were the same or different by licking left or right. Using generalized linear modeling across large-scale acute recordings, we found that odor information was strongest in olfactory areas, whereas decision-, choice-, and action-related signals were broadly distributed. Population analyses revealed that match/non-match information was prominent in olfactory regions, including the anterior olfactory nucleus, whereas left/right choice signals were stronger in motor-related regions such as anterior-lateral motor cortex. Orbitofrontal and prefrontal cortices carried mixed representations. QR decomposition showed that decision and choice signals occupied largely orthogonal dimensions, suggesting that perceptual decision variables can be represented separately from motor output. To examine how these representations develop during learning, we performed chronic Neuropixels recordings targeting anterior olfactory nucleus, orbitofrontal cortex, and anterior-lateral motor cortex. Decision signals were present in the anterior olfactory nucleus early in training, whereas decision-related representations emerged, strengthened, and stabilized in orbitofrontal cortex and anterior-lateral motor cortex as performance improved. In contrast, choice signals increased and stabilized across all three regions. Together, these results show that olfactory decision-making relies on distributed but dissociable neural dynamics. Rather than being generated only in higher-order cortical areas, perceptual decision signals are already present in early olfactory circuits and are progressively reorganized across downstream regions during learning, providing a circuit-level view of how sensory information is flexibly transformed into action.

Disclosures: J. Do: None. **D. Lee:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.04/II21

Topic: I.03. Decision Making

Title: Neural and Computational Mechanisms of Social Trade-Off Decisions Under Foraging Constraints

Authors: *S. POWAR, E. TURE, D. KVITSIANI, E. DEMIR;
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Abstract: Animals constantly make trade-offs in how they allocate limited time. Time spent obtaining essential resources such as water cannot also be spent interacting with others. Yet little is known about how the brain balances social opportunities against biological needs in real time. Understanding this process is important for explaining flexible decision-making and may provide insight into conditions in which reward-guided or social behavior becomes inflexible, including addiction, autism spectrum disorder, and obsessive-compulsive disorder. To study this question, we developed a social-foraging task in which mice repeatedly choose between obtaining water and interacting with another mouse. Social interaction carries a measurable cost because it requires travel and delays access to water. This design allowed us to quantify how animals balance social reward against homeostatic need. We used dwell time as a temporal measure of preference and developed computational models to estimate the value mice assigned to social partners while accounting for the opportunity cost of missed water rewards. Across approximately 40,000 behavioral trials, mice showed stable and consistent preferences for specific social partners, supporting the existence of structured social valuation. These preferences shifted when the value of water changed, indicating that social behavior is flexible and depends on current physiological needs. Mice also adjusted both interaction duration and movement speed when the cost of social interaction increased. Together, these findings suggest that animals may evaluate competing rewards using time as a common currency. The computational models explained trial-by-trial choices, social interaction times, and movement patterns across experimental conditions. We are also investigating the neural circuits that support these decisions, focusing on connections between the orbitofrontal cortex and medial amygdala, regions implicated in reward processing and social behavior. Preliminary findings indicate that medial amygdala neurons carry information about specific social partners, while orbitofrontal cortex activity reflects the trade-off between social value and water value. By combining behavioral experiments, computational modeling, optogenetics, and neural recordings, this work provides a framework for understanding how animals allocate time between social interaction and essential resources. These findings may help reveal how the brain balances competing motivations and why this process can break down in disorders affecting reward and social behavior.

Disclosures: S. Powar: None. **E. Ture:** None. **D. Kvitsiani:** None. **E. Demir:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.05/II22

Topic: I.03. Decision Making

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Taylor Family Institute at Washington University in St. Louis

Title: Ventral striatum astrocytes contribute to reinforcement learning

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Abstract: Reinforcement learning (RL) describes the processes by which agents or organisms learn, through trial and error, to predict and take actions that maximize cumulative reward. Different aspects of RL are thought to be dependent on functionally heterogenous striatal circuits. Mounting evidence show that astrocytes can actively regulate neuronal function in these circuits. They can modulate up to hundreds of thousands of synapses per cell through astrocytic calcium dynamics (ACD) that can occur on a spectrum of spatiotemporal scales. In theory, astrocytes could uniquely contribute to neuronal circuits by helping to address a key function required for cognitive operations: adaptively regulating variability within local circuits to produce stable representations to guide behavior. However, whether and how astrocytes support specific behavioral computations in RL-guided behavior across striatum is still poorly understood. To start to assess this question, we attenuated astrocyte calcium activity across different subregions of striatum while animals performed a RL-dependent probabilistic reversal task. This computationally tractable task allowed us to model the effects of ACD attenuation within a normative learning framework. We found that attenuation of ACD in DMS and DLS had relatively little impact on key reinforcement learning parameters, such as on learning rate and inverse temperature (decision noisiness). In contrast, VS ACD attenuation decreased inverse temperature (increasing decision noisiness) and impaired reward-guided choice performance, specifically by reducing win-stay behavior. Using fiber photometry to monitor ACD during RL revealed that VS ACD reflected model inferred reward prediction errors (RPEs), for many seconds after the outcome, until the start of the next trial. We built a biologically constrained circuit model of neuron-astrocyte interactions to assess how astrocyte encoding of RPE learning signals could support RL-guided decision-making. In both photometry-obtained ACD and in our circuit model, trial-by-trial ACD fluctuations predicted trial-by-trial choice variability, particularly in win-stay behavior. In-silico experiments suggested that choice performance and win-stay behavior could be mediated by astrocytes averaging and sharing dopaminergic RPE inputs across MSN populations. These findings highlight a specific role of ACD in RL through the regulation of decision noisiness and win-stay stability, and they generate novel hypotheses for how astrocytes modulate the circuits underlying value-based decision-making and cognition.

Disclosures: J. Pai: None. **F. Sogukpinar:** None. **K. Ogasawara:** None. **G.J. Smith:** None. **F. Fiocchi:** None. **Y. Dai:** None. **Y. Wu:** None. **M.J. Frank:** None. **S. Ching:** None. **F. Lucantonio:** None. **T. Papouin:** None. **M. Pignatelli:** None. **N. Hiratani:** None. **I.E. Monosov:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.06/II23

Topic: I.03. Decision Making

Title: A "Mixture of Experts" for decision making in primate frontal and parietal circuits

Authors: *R. READ[1], E. LOUT[2], V. SADASIVAN[1], M. MOLL[1], H. M. STEALEY[4], J. A. LEWIS-PEACOCK[5], T. W. ELSTON[3];
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Abstract: Flexible decision making is essential for intelligent behavior and is profoundly disrupted in psychiatric disorders. What are the computational processes and neural mechanisms that enable such flexible decision-making? Inspired by recent advances in AI, we pursued the hypothesis that the brain operates as a "mixture of experts" - maintaining specialized neural circuits for different types of decisions - and that the final decision reflects a weighted contribution of these multiple decision circuits.
As a first test, we trained a non-human primate to perform both a value-based choice task and a classic dot-motion perceptual decision task. We made Neuropixel recordings from the orbitofrontal cortex (OFC) during the performance of both tasks. We found that OFC selectively carried information related to value-based decisions but never rose above chance during the perceptual decision task. This suggests that the different types of decisions are mediated by at least partially dissociable neural circuits - consistent with a “mixture of experts” architecture. We then developed a new behavioral task where both human (N = 150) and non-human primates (N = 2) flexibly shifted between making value-based and perceptual decisions within the same session. This new task used the exact same stimuli for both decision types and subjects were explicitly cued whether to make a value-based or perceptual decision on each trial. This enabled us to hold the visual input and motor responses constant while varying the underlying decision process. We then modelled choice behavior as a weighted sum of distinct “value” and “perceptual” decision modules. This model provided an excellent account of both human (R2 = .92) and monkey choice patterns and, critically, was able to predict psychiatric symptom severity related to obsessive compulsive disorder and alcohol abuse. This suggests that these disorders, in part, reflect a failure in the brain’s ability to flexibly modify the weight given to different decision systems. Currently, we are making Neuropixel recordings from frontal and parietal decision regions in monkeys to reveal how the flexible reweighting process captured by our “mixture of experts” model is realized in neural circuits.

Disclosures: R. Read: None. **E. Lout:** None. **V. Sadasivan:** None. **M. Moll:** None. **H.M. Stealey:** None. **J.A. Lewis-Peacock:** None. **T.W. Elston:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.07/II24

Topic: I.03. Decision Making

Title: Feature-based valuation and its impairment in psychiatric disease

Authors: *M. G. MOLL[1], R. K. READ[2], H. M. STEALEY[2], T. W. ELSTON[3];
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Abstract: Our decisions are only as good as the information on which they are based — and yet irrelevant (or harmful) information routinely drives peoples' choices in ways that undermine their goals. What are the computations and mechanisms enabling the brain to prioritize relevant over irrelevant information during decision-making?
Answering these questions required developing a task that measures how individuals weigh relevant versus irrelevant sensory information during decision-making. Each trial began with a cue directing attention to either the color or shape of two upcoming choice options. Different colors and shapes are associated with different reward values. The key trials are where the higher-reward color and higher-reward shape belong to different options, meaning the best choice depends on whether color or shape is relevant.
We found that both humans (N = 450) and non-human primates (N = 2) struggle to ignore irrelevant features - irrelevant feature values actively interfere with and can override relevant ones, leading to suboptimal choices. We modelled this interference as a weighted sum of relevant and irrelevant features. This model could explain individual differences in human behavior (R^2 = .82) and, critically, could predict human psychiatric symptom severity related to substance abuse and obsessive-compulsive disorder. This suggests that these disorders, in part, reflect impairment in the brain's ability to appropriately weigh relevant versus irrelevant sensory information when assigning value to choice options - a computation we term feature-based valuation.
Now, using high-density Neuropixels recordings in monkeys, we are working to understand how feature-based valuation is realized in neural circuits.

Disclosures: M.G. Moll: None. **R.K. Read:** None. **H.M. Stealey:** None. **T.W. Elston:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.08/II25

Topic: I.03. Decision Making

Title: Dissociating the relationship between time perception and decisions to delay gratification

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Abstract: The ability to forgo an immediate reward in favor of a larger, later one is central to healthy decision making - yet some people struggle to delay gratification. A prominent theory proposes that people with faster internal clocks experience delays as subjectively longer and more costly, leading them to discount future rewards more steeply. Here we test this theory's central prediction by asking whether individual differences in time perception can explain individual differences in temporal decision-making. We recruited 226 participants to complete tasks measuring time perception and delay sensitivity across experiential and hypothetical decisions. We found no relationship between time perception and temporal decision-making. We also found that survey and task-based measures of temporal discounting are unrelated and that neither measure predicts real-world timing-related behaviors. Our findings indicate that time perception and temporal decision-making derive from dissociable cognitive processes and that standard laboratory measures of discounting have limited ecological validity. We suggest that foraging paradigms, which embed time-reward tradeoffs in naturalistic behavioral contexts offer a promising path toward more ecologically valid and mechanistically tractable approaches to understanding how the brain trades off time and reward during decision-making.

Disclosures: I.J. George: None. **M.G. Moll:** None. **R.K. Read:** None. **H.M. Stealey:** None. **T.W. Elston:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR073.09/II26

Topic: I.03. Decision Making

Title: An open-source, 3D-printable drive system for acute Neuropixels recordings in awake, behaving primates

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Abstract: The advent of the primate Neuropixels probes has enabled researchers to simultaneously monitor the spiking activity of hundreds of neurons using a single probe. These cutting edge probes enable qualitatively different types of insight into the neural dynamics of cognitive processes. However, these probes are incredibly fragile and, as yet, there is no standard approach for safely and accurately inserting them into deep brain structures. We overcame this challenge by developing a modular, 3D-printable drive system that enables simultaneous, safe,

and accurate insertion of multiple Neuropixels probes into the brains of awake, behaving primates.
A key feature of the drive system is that both the probe and the guide tube are independently drivable. The probe and guide tube are both actuated along a linear rail, ensuring that that probe and guide tube remain aligned at all possible insertion depths - dramatically reducing the likelihood of probe breakage in the brain. This feature also maximizes the length of the probe that can be inserted into tissue, as the top of the guide tube can be driven to have an extremely low profile to the dura. In turn, this enables the probe base to be lowered within 4 millimeters of the dura.
While the base drive model is hand-driven, we have also developed a small, motorized attachment for precise, automated lowering of the probes. The motors are controlled via an Arduino through an intuitive GUI in which the experimenter can set the target depth and lowering speed for the guide tube and probe independently.
Our drive system has been validated to be accurate within 1 millimeter at a depth of 42 millimeters. Here, we also present our drive system validated in vivo with example recordings from the orbitofrontal cortex of a rhesus macaque monkey performing a decision-making task. All of the CAD design files and the GUI software are publicly available.

Disclosures: H.M. Stealey: None. **T.W. Elston:** None.

Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

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Topic: I.03. Decision Making

Support: NIH MH123661
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Title: Explore and exploit state representations in mouse mPFC neural activity during decision making

Authors: D. MUELLER[1], **N. GLEWWE**[2], S. WEIR[2], A. CHERICONI[5], A. S. WIDGE[3], M. V. CHAFEE[7], B. EBITZ[8], S. R. HEILBRONNER[6], *N. M. GRISSOM[4];
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Abstract: In changing environments, decision making engages explore-exploit tradeoffs, balancing choices between exploration of options to learn their values, and repeated execution of a choice. Disruptions in explore-exploit balance have been associated with neuropsychiatric risk and resilience. As such, understanding the neural mechanisms responsible for sustaining and switching between explore-exploit states has become a high value target in preclinical models.

Previous research has identified that medial prefrontal cortex (mPFC) circuits are responsible for flexible decision making and mPFC activity might mediate the tradeoff between exploration and exploitation in non-human primates. To further characterize the role mPFC neurons play in flexible decision making and explore-exploit balance in mice, we used free-moving in-vivo electrophysiology to record mPFC single unit activity in mice (129/b6j F1, 4F/4M) during a two-armed restless bandit task. Silicon probes (Cambridge Neurotech, 2 shank, 32 channels) were implanted unilaterally, directed to anterior cingulate and prelimbic cortex (AP +1.8, ML +/- 0.30, DV -2.05). The restless bandit task encourages periods of exploration and exploitation as the reward probabilities of each choice vary randomly and independently across trials. Explore/exploit states were identified throughout restless bandit behavior using a hidden Markov model (HMM). Consistent with previous research, we identified single units in mPFC that encode outcome, valence, and choice. We additionally identified distinct neural ensemble representations of explore and exploit behavioral states which are differentially decoded from mPFC activity using a time-resolved linear discriminant analysis. Surrounding state transitions, we find more correlated activity in exploit state labeled trials on either side of explore-exploit state transitions, suggesting greater neuronal synchrony in exploit states. Current analyses investigating putative cell identities using waveform analysis suggest that the neurons preferentially activated in each state differ in firing rate and neuronal subtype. Together, these results suggest that in addition to encoding outcome, valence, and choice, distinct mPFC neural representations contribute to sustaining and switching between explore-exploit states.

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Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

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Title: Striatal subregions exhibit distinct dopaminergic signatures during explore-exploit state transitions

Authors: *M. M. POROD[1], C. S. CHEN[2], A. PAULSON[2], E. M. GRIGSBY[3], B. A. EBITZ[4], B. T. SAUNDERS[1], N. M. GRISSOM[2];
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Abstract: Flexible decision making requires a tradeoff between exploiting options believed to be rewarding and exploring amongst unfamiliar options to learn their value. Despite its importance in adaptive behavior, the neural mechanisms governing the explore-exploit tradeoff remain unclear. However, a growing body of evidence indicates that dopamine-through its established functions in reward learning, motivation, and action selection-plays a critical modulatory role. Here, we examined dopamine signaling dynamics in the nucleus accumbens (NAc) and dorsomedial striatum (DMS) as mice transitioned between exploratory and exploitative strategies during decision making. Male and female B6129SF1/J wildtype mice (n=20, 9M/11F) were trained on a touchscreen-based spatial two-arm restless bandit task in which the probability of reward for each choice drifted gradually and independently throughout the session. A hidden Markov model was used to identify latent exploratory versus exploitative choice sequences, or states. Using fiber photometry with the dopamine biosensor dLight1.3b, we recorded dopamine signaling in the NAc and DMS as mice engaged in the restless bandit task. We found that dopamine signaling in both NAc and DMS was significantly state-modulated during distinct behavioral epochs. NAc dopamine exhibited enhanced reward-prediction error-like dynamics during feedback cue presentation in exploratory states, consistent with the heightened learning demands attributed to exploration. In contrast, DMS dopamine exhibited a transient increase during exploratory choices that was not observed for exploitative choices, suggesting a role in flexible action selection. These region-specific patterns were particularly accentuated surrounding the transition between exploratory and exploitative states. Ongoing work includes adapting linear modeling approaches to parse the contributions of cognitive state, reward history, and motor patterns to dopamine signaling dynamics. Together, these findings reveal region-specific dopaminergic contributions to explore-exploit balance and provide new insights into how striatal subregions facilitate flexible decision making strategies.

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Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

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Topic: I.03. Decision Making

Support: NIH Grant F32 DA065393 (SEA)
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Title: Get over it! Characterization of neural signals in NAc and anterior insula in rats performing a novel multistep perseverance task

Authors: *S. ASHTON[1], E. PARANZINO[1], A. GUPTA[1], B. OSUALA[1], A. G. SPERA[2], M. R. ROESCH[3];
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Abstract: Why is starting over harder than starting up? How do you get over failures that set you back to square one? What brain areas encode this information? To start to address these questions we have established a novel "Multi-Step Perseverance Task" (MSPT) to explore the psychological constructs that mediate how effort, perseverance and resilience influence the drive towards a goal that requires multiple steps to achieve and often results in setbacks along the way. In the task, rats respond to sequential cues, but "fall" back earlier in the sequence when they fail to maintain the nosepoke hold long enough. The "fall distance" varies depending on the point in the sequence at which the mistake was made, allowing for comparison between harder and easier fall sequences that occur after more or less work has been put into a sequence. Behaviorally, we find that rats speed up as they move through a sequence, but slow down directly after errors. Moreover, rats make more mistakes on trials where they will ultimately poking in the wrong port, failing to obtain reward. After this kind of unrewarded error, rats are slower to reengage in the task and less likely to see their next trial through to reward when they do start again. We are recording from single neurons in the nucleus accumbens (NAc) and anterior insula (AIC) as rats perform this task. A main function of NAc is to bias the direction and intensity of behavior to increase the probability of reward, and we have previously found that NAc neurons track reward history, perhaps promoting proactive action selection following successes. We will examine activity of NAc ensembles at the beginning of trial sequences that are preceded by rewarded and unrewarded trials, as well as during cues and actions as the rat progresses through a sequence towards reward obtainment. AIC also provides a compelling target as it has been linked with an extraordinary variety of functions, including addiction vulnerability, emotional processing and myriad decision-making processes. We will ask whether activity of AIC ensembles in response to mistakes scales with the severity of the error (e.g., a hold error at the beginning versus end of a trial sequence, or an unrewarded wrong poke sequence) or relates to restart readiness after mistakes. Overall, the MSPT is unique from other tasks that manipulate reward probability, magnitude or effort independent of the rat's performance in that it asks the rat to find a balance between the drive to keep going and an appropriate level of inhibition to prevent errors. This work seeks to provide novel insight into the ability to keep going and try again after mistakes, which has broad relevance to psychiatric disorders like addiction.

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Poster

PSTR073: Orbitofrontal, Corticolimbic Circuits, and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR073.13/II30

Topic: I.03. Decision Making

Support: NIH Intramural Research Program

Title: Developmental disruption of the medial pulvinar impairs thalamo-prefrontal functional connectivity and related cognition in marmosets

Authors: *K. MARCHE[1,2], J. PHAN[2], J. A. BOURNE[2];
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Abstract: The medial pulvinar is densely interconnected with prefrontal cortex and is well placed to influence the maturation of cognitive control. To test this, we produced early-life excitotoxic lesions of the medial pulvinar in marmosets and assessed prefrontal-dependent cognition using the spatial delayed recognition span task. In this task, animals selected novel stimuli across increasing spans with intervening delays, and recovery trials provided a distinct context in which error correction could be examined. Behaviour was characterised across multiple contexts, including span-dependent difficulty, delay sensitivity and recovery after errors. We quantified success rate, response and release times, touch accuracy, and within-trial reward processing using Q-learning models of reward prediction error. Animals with medial pulvinar lesions showed robust and persistent impairments. Relative to controls, they made more errors across all stages of the task, became less accurate as span increased, and were more vulnerable to delays between spans. They also responded more quickly overall, appeared less likely to process feedback, and showed more volatile reward-related updating. In recovery trials, lesioned animals were markedly less able to correct errors when given the opportunity, consistent with impaired cognitive control and error monitoring. To identify behavioural determinants of performance, we used linear regression analyses to determine which measures best predicted individual success. We will also present resting-state fMRI evidence that early medial pulvinar disruption alters functional connectivity within prefrontal-centred networks, and we examine whether these connectivity changes correlate with behavioural characteristics. Together, these findings indicate that intact medial pulvinar function during development is necessary for the normal maturation of prefrontal circuits supporting working memory, feedback monitoring and flexible control.

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Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Topic: I.03. Decision Making

Support: NIH Grant EY032999
CAREER award 2146369

Title: How history manifests in the macaque cortical hierarchy

Authors: ***J. MOON**[1], Z. M. BOUNDY-SINGER[2], J. A. CHARLTON[3], R. L. T. GORIS[1]; [1]The Univ. of Texas at Austin, Austin, TX; [2]MIT, Cambridge, MA; [3]Princeton Univ., Princeton, NJ

Abstract: Many sensory-guided behaviors rely on three distinct computational operations: sensory measurement, perceptual interpretation, and motor planning. It is well known that recent experience strongly influences sensory-guided behavior, yet it remains unclear how history manifests across these successive computational operations. To investigate this, we studied neural population activity recorded from the visual and prefrontal cortices of macaque monkeys while they performed a perceptual decision-making task. The animals judged whether a visual stimulus was tilted clockwise or counterclockwise relative to vertical and communicated their decision with a saccadic eye movement. As in prior human studies, perceptual choices of each monkey exhibited robust attraction toward previous choices and repulsion away from previous stimuli. How does this behavioral pattern emerge from the underlying neural activity in cortical circuits? To address this question, we analyzed the one-dimensional linear component of neural population activity in V1 and FEF that pertains to the formation of monkeys' choices. This population analysis revealed distinct transformations of sensory information across sensory, perceptual, and motor spaces. Neural activity in all three subspaces was systematically influenced by momentary sensory evidence. Interestingly, stimulus and choice history exerted a distinct influence on neural activity. In particular, choice history effects emerged before stimulus onset and increased during stimulus presentation in perceptual space, consistent with the interpretation that it reflects a perceptual expectation. Analogous choice history effects were evident in sensory space before and during stimulus presentation. In contrast, stimulus history effects only emerged after stimulus onset in perceptual space and were absent in sensory space. Lastly, motor representations expressed history effects only late in the trial, suggesting that motor space simply inherits the biases formed in sensory and perceptual spaces. Together, these results reveal how history-dependent behavior emerges from structured dynamics in neural population activity across the cortical hierarchy. More broadly, our work illustrates how a targeted analysis of neural population activity in different brain regions can reveal the neurobiological basis of fundamental brain computations.

Disclosures: J. Moon: None. **Z.M. Boundy-Singer:** None. **J.A. Charlton:** None. **R.L.T. Goris:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.02/II32

Topic: I.03. Decision Making

Support: Intramural Research Program of NIMH

Title: Medial Septal Galanin Circuitry in Cognition and Behavior

Authors: *I. AZINGE[1], Y. CHUDASAMA[2];
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Abstract: The medial septum diagonal band of Broca (septal complex) is a basal forebrain structure critical for learning and memory. It contains diverse neuronal populations and several neuropeptides, including galanin. Although altered galanin signaling is associated with cognitive dysfunction, the underlying circuitry remains poorly understood. Here, we characterized septal galanin circuitry and examined its role in cognitive, social and emotional behavior.
To selectively target galanin expressing neurons, we generated a Galanin-Cre knock-in rat line (LE-Gal$^{em2(cre)Davis}$; RRRC # 001028). Brain-wide mapping revealed dense galanin innervation within the septal complex. Retrograde viral tracing showed that most galinergic inputs within the septal complex originate locally, with additional projections arising from the paraventricular thalamic nucleus and the locus coeruleus. We next characterized the cellular distribution of galanin receptors in the septal complex using fluorescent in situ hybridization. Both GalR1 and GalR2 were predominantly expressed on GABAergic neurons, whereas GalR2 alone was expressed on cholinergic neurons suggesting receptor-specific modulation of septal circuitry by galanin. To examine the functional role of these receptors, selective agonists and antagonists were infused into the septal complex, but we found no detectable effects on cognitive, social or behavioral measures.
Given these negative finding, we next assessed the broader contribution of the septal complex to behavior using neurotoxin lesions. Lesioned rats exhibited impaired learning, and responded more rapidly, consistent with increased impulsive responding. To further evaluate impulsivity, rats were tested on a non-spatial delay discounting task in which a response to one stimulus always provided a 1-pellet reward, while the other stimulus always resulted in the delivery of a 4-pellet reward. Despite multiple exposures to trial blocks of 0, 8, 16 and 32s delays to reward, lesioned rats failed to prefer the large reward, even when there was no delay to reward (0s delay trials). When the delay was removed across all trial blocks, the lesioned rats regained their preference for the large reward, suggesting that the septal lesion enhances reward devaluation following delayed reward rather than producing a generalized deficit in reward preference. Lesioned animals also showed increased locomotor activity and aggression, implicating the septal complex in social and emotional regulation. Future studies will use chemogenetic approaches to inhibit septal galanin circuits to determine their specific contribution to these behavioral functions.

Disclosures: I. Azinge: None. **Y. Chudasama:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.03/JJ1

Topic: I.03. Decision Making

Support: NIMH IRP ZIAMH002784

Title: Effects of prior experience on social aggression are dependent on adult hippocampal neurogenesis

Authors: *M. C. TSUDA, H. A. CAMERON;
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Abstract: In the dentate gyrus of the hippocampus, new neurons are continuously generated throughout adulthood. Functionally, adult neurogenesis plays a role in attention, motivation, and responses to stressors and unpredictability. We recently demonstrated that suppressing neurogenesis in male mice decreases social aggression, implicating adult neurogenesis as an important mediator of social behaviors. Here, we further investigated the role of adult-born neurons in modulating social behaviors. Previous experiences, whether positive or negative, have the potential to shape subsequent behaviors, such as impairing or enhancing learning and memory tasks and anxiety-related behaviors. However, it is still unclear how prior experiences impact social behavior and how adult-born neurons are involved in these changes. To suppress adult hippocampal neurogenesis, we treated 8-week-old male transgenic mice expressing the herpes simplex virus thymidine kinase under a GFAP promoter with the anti-viral drug valganciclovir. After 8 weeks of drug treatment, mice with (WT) and without ongoing adult neurogenesis (TK) were tested for social aggression following a positive fighting experience or a negative frustrative nonreward experience (omission of an expected food reward). We found that positive fighting experiences increased social aggression levels in TK, but not WT male mice, whereas negative frustrative experiences heightened aggression in WT, but not TK mice, suggesting that prior experiences modify aggression levels in male mice, but the changes are dependent on adult neurogenesis. Findings from these studies suggest that prior experiences - whether it be aversive or appetitive- influence social behaviors and adult hippocampal neurogenesis may play a role in these behavioral changes.

Disclosures: M.C. Tsuda: None. **H.A. Cameron:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.04/JJ2

Topic: I.03. Decision Making

Title: Sex differences in the effects of acute wheel running on stress, spatial memory, anxiety-like behavior, and cognitive bias

Authors: *T. J. SCHOENFELD[1], A. WACHTEL[3], E. CASTANEDA[2], J. DAVIS[1], A. DEVOLVE[2], D. GUEVARA[2], T. MOORE[2], M. PARROTT[2], S. ROBERTS[2];
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Abstract: Aerobic exercise is a physiological stressor but can buffer responses to subsequent stressors and alter cognition and affect. Although the effects of long-term running over multiple days and weeks are widely tested in experimental rodents, the impact of acute, single bouts of running are underexplored. Two particular gaps in studying acute running are its potential stress-coping abilities and potential sex differences in its effects. Therefore, we tested the effects of a single bout of voluntary wheel running (15 min) on spatial working memory, anxiety-like behavior, and cognitive bias in adult male and female Long-Evans rats using a within-subjects design. Rats were tested under baseline conditions and following acute loud music stress, with or without post-stress running. Spatial working memory was assessed on a radial arm maze (RAM), anxiety-like behavior on the elevated plus-maze (EPM), and cognitive bias using a reward-based judgment task. In males, acute stress increased latency to complete the RAM without affecting errors, suggesting increased caution, which running reversed. Running also increased open-arm exploration on the EPM at baseline and reduced latency during ambiguous trials on the cognitive bias test, consistent with reduced caution or more optimistic bias. In contrast, females showed impairments following both stress and running, with increased latencies and errors on the RAM. Although running increased open-arm exploration on the EPM, it slowed responses during ambiguous trials on the cognitive bias test, indicating increased caution or pessimistic bias. Corticosterone increased following stress in both sexes and even further with running in only females. These results suggest that acute exercise alters behavior primarily by modulating cautious decision-making under stress or uncertainty rather than improving memory accuracy, and that these effects are strongly sex-dependent, with exercise reducing caution in males but mimicking stress effects in females.

Disclosures: T.J. Schoenfeld: None. **A. Wachtel:** None. **E. Castaneda:** None. **J. Davis:** None. **A. Devolve:** None. **D. Guevara:** None. **T. Moore:** None. **M. Parrott:** None. **S. Roberts:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.05/JJ3

Topic: I.03. Decision Making

Support: NIMH IRP ZIAMH002784

Title: Hippocampal c-Fos expression following social aggression in male mice without adult hippocampal neurogenesis

Authors: *L. R. GREENSTEIN, M. C. TSUDA, H. A. CAMERON;
NIMH, Bethesda, MD

Abstract: Throughout life, new granule cells are born in the dentate gyrus and subsequently integrate into the hippocampal circuitry. We recently demonstrated that adult male mice lacking adult neurogenesis display reduced intermale aggressive behaviors, implicating adult hippocampal neurogenesis as an important mediator of social aggression. In the present study, we investigated aggression-induced neuronal activity specifically in the hippocampus and evaluated whether suppression of adult neurogenesis alters this activity. To eliminate adult hippocampal neurogenesis, we used a pharmacogenetic animal model in which male mice express the herpes simplex virus thymidine kinase under the control of GFAP promotor. Starting at 8 weeks of age, mice with (TK) and without (WT) the transgene were treated with the antiviral drug, valganciclovir, to eliminate the birth of new neurons and remained on treatment for the duration of the study. Following 8 weeks of drug treatment, WT and TK male mice were single-housed for one week, and then novel intruder mice were placed into their cages for resident-intruder paradigm aggression testing six times over two weeks. Mice were perfused 90 min after the final aggression test. Additional WT and TK male mice never exposed to aggression testing were perfused as controls. Brains were sectioned through the entire extent of the dorsal and ventral hippocampus, immunolabeled for c-Fos (a marker for neuronal activity), and imaged on the Zeiss Axioscan 7 digital slide scanner. We are quantifying c-Fos positive cells in the dorsal and ventral dentate gyrus, CA3, CA2, and CA1 subregions of the hippocampus. Differences in hippocampal c-Fos expression between WT and TK mice should provide valuable insight into the ways adult-born neurons alter hippocampal network activity in response to social stimuli. Findings from these studies will add to the understanding of how adult-born neurons impact the hippocampal networks involved in instigating intermale aggression.

Disclosures: L.R. Greenstein: None. **M.C. Tsuda:** None. **H.A. Cameron:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.06/JJ4

Topic: I.03. Decision Making

Support: NIMH IRP ZIAMH002784

Title: Suppression of adult hippocampal neurogenesis modifies approach-avoidance behavior in a novel thermal conflict task

Authors: *A. P. SWIERCZ[1], S. CAMPBELL[3], H. A. CAMERON[2];
[2]NIMH, [1]NIH, Bethesda, MD; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: When difficult decisions must be made, the hippocampus contributes to behavioral conflict resolution by modulating the inhibition of dominant behavioral responses. The dentate

gyrus, unique for its ability to produce new neurons into adulthood, plays a key role in this process. But it is currently unclear whether adult neurogenesis is directly involved in difficult decision-making, and which aspects of decision-making are affected by new neurons. Here, we introduce a novel behavioral task to examine the role of adult-born neurons in conflict-based decision-making following the ablation of neurogenesis in adult male rats. Neurogenesis was eliminated by 8 weeks of oral valganciclovir treatment in transgenic Long-Evans rats expressing the herpes simplex virus thymidine kinase (TK) under control of the glial fibrillary acidic protein (GFAP) promoter. Wild type (WT) littermates lacking the transgene served as controls. In the cold suppressed feeding task, animals were placed in an arena with a large cold zone (variable temperature) and a small warm zone (25C). A pellet dispenser in the cold zone rewarded nose pokes on a VI-8 reinforcement schedule. During the training phase, when both zones were set to 25C, both genotypes earned a similar number of pellets. However, as cold zone temperatures were decreased, creating an approach-avoidance conflict, WT controls spent less time in the cold zone and earned fewer pellets than animals lacking adult-born neurons. These findings indicate that adult-born neurons influence decision making in approach-avoidance conflicts and highlight the cold-suppressed feeding task as a valuable tool for investigating hippocampal neurogenesis.
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Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.07/JJ5

Topic: I.03. Decision Making

Support: Nu Rho Psi Undergraduate Research Grant

Title: Tunnel vision: How adult neurogenesis impacts anxious decision-making in adult rats

Authors: *E. C. JOHNSON[1], M. GONZALEZ[1], H. A. CAMERON[2], T. J. SCHOENFELD[1]; [1]Belmont Univ., Nashville, TN; [2]NIMH, NIH, Bethesda, MD

Abstract: Anxiety is increasingly prevalent, emphasizing the need for translational animal models that capture not only heightened threat sensitivity but also the difficulty individuals face when adapting behavior once previously threatening cues become safe. Traditional rodent anxiety tests primarily measure reduced exploration, offering an incomplete model of this flexibility component, whereas adult neurogenesis in the hippocampus, a region implicated in anxiety regulation, negative feedback of stress, and conflict resolution, may support adaptive decision-making under stress. This project examined how adult hippocampal neurogenesis influences anxiety-related decision-making using adult male wildtype (WT) and GFAP-TK transgenic (TK) rats (n = 9 each), the latter exhibiting inhibited neurogenesis in adulthood

following valganciclovir treatment. Rats completed a modified t-maze task in which there is a short and long path choice to reward (long path is 4x longer). After forming a short-path preference, rats were restrained in Plexiglas tubes for nine hours over three days. After completion of stress, rats again completed the t-maze, but an open restraint tube was placed along the short path, requiring rats to pass through it to obtain reward through that path. Finally, rats went through extinction training with the restraint tube in their home cage and were retested in the t-maze. Both WT and TK rats learned to prefer the short route and avoided the short route following stress similarly. After extinction, a genotype effect showed WT rats went back to choosing the short route, but TK rats were mixed in their decisions, suggesting a failure for TK rats to adapt in their decision-making. However, across phases, TK rats changed their route choice less, had fewer turnarounds in the maze environment, and made a final path evaluation quicker, suggesting their decision-making was less deliberate than WT controls overall. Corticosterone was measured in blood samples following post-stress and post-extinction trials, which associated with maze behavior for both WT and TK rats. Lastly, dendritic morphology was analyzed using a Golgi-Cox stain in both WT and TK rats, replicated atrophy effects of chronic inhibition of neurogenesis within the dentate gyrus and CA3 regions of the hippocampus. By integrating behavioral and neural measures, this project adds to how adult neurogenesis contributes to adaptive decision-making in anxious contexts, offering translational insights into the mechanisms relevant to both the development of anxiety disorders and exposure-based treatments.

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Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.08/JJ6

Topic: I.03. Decision Making

Title: Synergistic roles of prelimbic corticostriatal neurons and direct pathway patch neurons in dorsal medial striatum during flexible decision-making in mice

Authors: *L. AMARANTE[1,2], E. ALBRECHT[2], A. HIGGS[2], V. CALIA-BOGAN[2], L. CHOU[2], A. LANGDON[2], V. A. ALVAREZ[2];
[1]NIH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Adaptive goal-directed behavior requires animals to use previous outcomes to guide future choice. An inability to adapt leads to inflexible behaviors such as compulsivity or perseveration, which are evident in many neuropsychiatric disorders. The corticostriatal circuit, specifically projections from the prelimbic cortex (PL) to the dorsomedial striatum (DMS), plays a key role in behavioral flexibility by integrating value information and guiding action selection. However, still unknown is the computation of how value estimates are used to guide rapid action

selection on a trial-by-trial basis. More specifically, what is the contribution from PL projection neurons to direct pathway D1-expressing medium spiny neurons (MSNs) in patches (aka striosomes) in this computation? D1 MSNs in patches receive strong input from PL, and have been shown to directly project to dopaminergic neurons in the substantia nigra. Therefore, we reason that D1 MSNs in patches are well positioned to not just receive value input from PL, but also to integrate relevant value signals from PL to promote the selection of actions via their direct projections to midbrain dopamine neurons, ultimately modulating dopamine signals that guide future choice. To investigate these questions, we simultaneously measured the activity of cortical projections and patch D1 MSNs in mice during a value-based decision-making task. Mice participated in a probabilistic reversal learning task as we made fiber photometry measurements of calcium signals in patch D1 MSNs (infusing a cre-dependent jrGeco1a into DMS of Pdyn-IRES-cre mice) and PL projection neurons to DMS (infusing Gcamp8s into PL). Bilateral optic fibers were implanted in DMS to measure calcium signals of PL terminal activity and patch D1 MSNs. Head-fixed thirsty mice made choices by licking to a left or a right water spout after a "go" cue onset. The probability of reward changes in a block-like manner to assess how mice use previous outcomes to guide future choice. Behaviorally, mice improved accuracy late in trial blocks, showing evidence of learning to choose the high probability spout quickly after a block switch. Both PL terminals in DMS and patch D1 MSNs show differential activity around 1) cue onset, 2) outcome (rewarded versus unrewarded trials), and 3) recent reward history and their expectation of obtaining reward. Interestingly, there are time course differences between PL terminals and D1 MSNs activity, which may reflect differential encoding of value by PL input and action selection by patch D1 MSNs. We are currently using computational methods to correlate both observable and latent behavior variables with fiber photometry signals.

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Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.09/JJ7

Topic: I.03. Decision Making

Title: Relating fiber photometry signals to behavior: Unique contribution of dopamine versus D1 MSN activity in dorsal striatum during flexible decision-making in mice

Authors: *E. ALBRECHT[1], L. M. AMARANTE[3], A. HIGGS[5], V. C. CALIA-BOGAN[6], L. CHOU[2], V. A. ALVAREZ[4], A. J. LANGDON[7];
[1]Natl. Inst. of Hlth., Bethesda, MD; [2]Natl. Inst. of Hlth., Washington DC, DC; [4]Lab. on Neurobio. of Compulsive Behaviors, [3]NIH, Bethesda, MD; [5]Natl. Inst. of Mental Hlth., Rockville, MD; [6]Natl. Inst. of Mental Hlth., Bethesda, MD; [7]Natl. Inst. of Mental Hlth., Natl. Inst. of Mental Hlth. Div. of Intramural Res., Bethesda, MD

Abstract: Inflexible decision-making is a defining symptom of neuropsychiatric disorders such as substance use and obsessive-compulsive disorders, motivating investigation into how different components of neural circuits guide behaviors in contexts where flexibility is beneficial. Previous work using behavioral tasks with dynamic changes in action-outcome associations showed that the activity of direct pathway D1-receptor expressing medium spiny neurons (D1 MSNs) in the dorsomedial striatum tracked temporal changes in action-outcome associations, suggesting encoding of action selection. In separate experiments, midbrain dopamine (DA) input to the striatum was shown to track differences in expected and actual reward outcomes, known as reward prediction error (RPE). However, robustly identifying how D1 MSN activity and DA signals influence each other in the striatum, and thus influence flexible behavior in complex tasks, is still an ongoing area of research. Therefore, in this study, we computationally probed correlations of the activity of D1 MSNs and DA signals with behavioral choices and task features during flexible decision-making. Thirsty, head-fixed mice performed a probabilistic reversal learning licking task in which they were trained to lick to an auditory cue, choosing between two spouts whose probability of distributing a water reward switched in a block-like manner within daily sessions. During these sessions, we measured calcium signals from striatal D1 MSNs using GCaMP8s and DA levels using dLight1.3b with fiber photometry recordings in the dorsomedial striatum. On average, D1 MSN activity and DA levels showed distinct responses to task-related features and reward outcomes throughout the task. In particular, a linear mixed-effects regression model of the trial-wise signal AUC in a time window up to 2s after the outcome time revealed that while D1 MSNs showed a significantly greater response in unrewarded versus rewarded trials, DA signals, on the other hand, were RPE-like, showing an increase on rewarded trials and a decrease on unrewarded ones. To expand these analyses, a multivariate computational model of the distinct timecourses of D1 MSN and DA responses to both time-locked task events and variably-timed behavioral events reveals the differential contribution of these features to the fiber-photometry signals and how they change as behavior adapts on the task. This work contributes to continued efforts investigating how DA interacts with direct pathway D1 MSNs within and across trials to regulate behavioral flexibility in mice.

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Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.10/JJ8

Topic: I.03. Decision Making

Support: NIMH Intramural Program

Title: Vector Autoregressive Regression with eXogenous (VARX) inputs to examine context and region dependent interactions between dopamine and acetylcholine in the mouse striatum

Authors: *L. P. CHOU[1], V. A. ALVAREZ[2], B. B. AVERBECK[1];
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Abstract: Dopamine (DA) and acetylcholine (ACh) are critical neuromodulators of striatal microcircuitry that influence action selection, reinforcement learning, and decision-making. Classically, they were thought to act by regulating fast glutamate and GABA neurotransmission. However, recent findings show that DA and ACh can directly influence each other. In striatal slices ex vivo, synchronized activation of cholinergic interneurons (ChI) was shown to trigger DA release through nicotinic receptors on DA axons; in the nucleus accumbens (NAc), selective ChI activation is sufficient to enhance phasic DA release. Other studies challenged this causal ACh / DA relationship by showing that ACh and DA are uncorrelated in vivo (Krok et al, 2023) and that DA inhibits ACh transients through D2 receptors in the ventrolateral striatum (VLS) during a reward-guided decision-making task (Chantranupong et al. 2023). By contrast, MacDonald et al. (2026) showed that paraventricular thalamic input engages ChIs in the NAc to regulate dopamine to promote safety learning in an active avoidance task. Our current study aims to characterize interactions between simultaneously recorded striatal DA and ACh and compare findings across striatal subregions and tasks. Further, we aim to assess whether temporally lagged regression models can identify task- and region-dependent DA-ACh interactions across fiber photometry datasets.To do so, we developed a vector autoregressive model with exogenous inputs (VARX), to predict DA and ACh fluorescence from each signal's recent history, the recent history of the other neuromodulator, and task events such as cue, reward, shock, or safety. We applied this framework to available datasets featuring dual DA/ACh measurements across two behavioral contexts: NAc during safety learning and VLS recordings during a decision-making task. Preliminary models captured substantial variance in both signals. Initial results suggest that DA-ACh coupling is similar across behavioral contexts.Because lagged regression is correlational, current analyses emphasize predictive structure rather than causality. Ongoing work will center models around behavioral epochs, harmonize sampling rates across datasets, evaluate multicollinearity and autocorrelation, and incorporate additional striatal datasets, including newly collected DA/ACh recordings if available. Together, this work provides a scalable analysis framework for comparing neuromodulatory interactions across tasks and for guiding future experiments combining DA and ACh sensors, behavior, and large-scale neural population recordings.

Disclosures: L.P. Chou: None. **V.A. Alvarez:** None. **B.B. Averbeck:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Topic: I.03. Decision Making

Support: Pew Innovation Fund, NIH R01 NS131229

Title: Probing decision formation and changes of mind in the mouse

Authors: *B. ZHAO[1], I. MORAN MARTINEZ[2], R. KIANI[2], N. LI[3];
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[3]Neurobio., Duke Univ., Durham, NC

Abstract: Flexible decision-making requires integrating information over time and revising a developing choice when new information shifts the balance of evidence. Psychophysical and electrophysiological studies in humans and nonhuman primates suggest that decision-makers can change their minds to correct potential mistakes. However, it remains unclear what factors drive such changes of mind (CoMs) on single trials and how post-commitment decision reversals are implemented in the brain. To address these questions, we developed an auditory discrimination task that allows tracking evolving decision states during evidence accumulation and subsequent revision after sensory information is no longer available. Mice discriminated the intensity of amplitude-modulated broadband noise and reported their choice by directional licking. Mean stimulus intensity varied across seven levels, and moment-to-moment intensity fluctuated stochastically, requiring mice to integrate evidence over time. A Go cue occurred 0.45-1.1 s after stimulus offset, imposing a delay epoch that separated evidence accumulation from motor response. Mice accumulated sensory evidence to solve the task and responded faster on easier trials. Psychophysical kernel analysis indicated that mice integrated evidence across the full stimulus period, with an early weighting bias. To examine decision dynamics on single trials, we recorded neural activity from anterior lateral motor cortex (ALM) using Neuropixels probes. We trained a linear decoder to estimate moment-by-moment decision states from ALM population activity. To link the decoded decision state to behavior, we terminated trials at different time points, forced mice to respond, and tested whether the decoded state predicted behavioral choice. The decoded decision variable accurately predicted choice throughout the trial, validating a time-resolved neural readout of decision state. Using this approach, we identified CoM events as rapid shifts in the decoded decision variable from one choice state to the other. During the stimulus epoch, CoMs were associated with rapid stimulus fluctuations favoring the alternative choice, indicating that sensory evidence can drive shifts in decision state. CoM events occurred more frequently under uncertain conditions and were more likely to result in correct choices, consistent with a corrective role reported in humans and primates. This work establishes a mouse model for studying the circuit mechanisms underlying decision formation and revision and provides an entry point for determining how distributed brain networks support flexible decision dynamics.

Disclosures: B. Zhao: None. **I. Moran Martinez:** None. **R. Kiani:** None. **N. Li:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Program #/Poster #: PSTR074.12/JJ10

Topic: I.03. Decision Making

Support: Pew Innovation Fund, R01MH127375

Title: Auditory evidence integration and covert changes of mind in macaque prearcuate gyrus

Authors: *I. MORAN MARTINEZ[1], B. ZHAO[3], N. LI[4], R. KIANI[2];
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Abstract: Discrimination of sensory stimuli relies on integration of information over time to improve accuracy. Neural correlates of this process have been observed in action-planning cortical regions, where activity tracks evidence supporting the preferred action. Yet it remains unclear how modularly these circuits are organized based on their sensory inputs. Lateral intraparietal area, frontal eye fields, and prearcuate gyrus (PAG), for example, represent decision variables in visual discrimination tasks and receive strong visual inputs. Here, we tested whether PAG represents evidence integration in an auditory task.

Two macaque monkeys discriminated the loudness of broadband noise whose amplitude was randomly modulated over time. Mean intensity varied across 11 levels, from 59.4 to 72.6 dB, centered on a 66 dB boundary. On each trial, monkeys heard the stimulus for 0.3-1 s, maintained the decision through a 0.45-1.1 s delay, and reported louder or softer by making a saccade to one of two targets on the screen. Performance improved with stimulus strength and duration. Psychophysical reverse correlation showed that choices were influenced more by early than late amplitude fluctuations, consistent with integration toward a bound.

We recorded simultaneously from tens of PAG neurons using Utah arrays. Individual neurons represented auditory evidence, with firing rates changing with stimulus strength. At the population level, PAG activity tracked moment-by-moment fluctuations in the decision variable during stimulus presentation, maintained this state during the delay, and transformed it into an action plan near movement. This single-trial estimate allowed us to identify putative changes of mind (CoMs) as rapid sign reversals of the neural decision variable. Approximately 10% of trials showed such reversals. CoMs occurred more often on difficult trials, corrective reversals were more common than error-generating reversals, and reversals occurred less frequently during late delay period.

Together, these results show that PAG represents auditory evidence integration and covert changes of mind, despite its association with visually-guided saccade planning. They suggest that action-planning circuits can support decision computations across sensory modalities.

Disclosures: I. Moran Martinez: None. **B. Zhao:** None. **N. Li:** None. **R. Kiani:** None.

Poster

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Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.13/JJ11

Topic: I.03. Decision Making

Support: K99DA062326
R01MH139681
R01DA065418
R01MH136272
NSF CAREER Award

Title: Contraction bias during value-based decision making

Authors: *C. E. GOLDEN[1], I. TRENARD[2], C. CONSTANTINOPLE[1];
[1]New York Univ., New York, NY; [2]New York Univ., New York, NY.

Abstract: A fundamental bias in working memory during perceptual decision making is contraction bias (or central tendency bias), in which a memory of a stimulus during recall regresses toward the mean of past stimuli. Whether contraction bias occurs during recall of reward values and affects value-based decision making is unknown. Using a two-alternative forced choice task where pairs of reward values were held constant for blocks of trials, we found the memory of the reward values faded over trials. Rats chose between reward offers with stable spatial locations: one varied in reward magnitude and the other varied in reward delay across blocks. Each block began with five forced choice trials to communicate the reward values for that block to the rat and then these parameters were held constant for 20 free choice trials. We found that rats quickly learned the reward values when the block changed and adjusted their choices accordingly. However, as time passed since choosing a reward, their choice probabilities were less sensitive to that reward's value in a manner that resembles contraction bias. For example, as time progressed since the rat chose the reward that varied in magnitude, their next choice depended less on the magnitude in that reward block, suggesting that the unchosen reward magnitude had been forgotten. Using a reinforcement learning model where the unchosen reward undergoes contraction bias, reducing information about the current reward state, we were able to recapitulate rat behavior. Furthermore, the strength of the bias varied over rats, suggesting that it is an accurate description of behavior and subject to individual differences. This suggests a strong connection between working memory mechanisms and reinforcement learning, and reveals individual differences in the quality of state representations over time across rats. Lastly, the dorsomedial striatum (DMS) is involved in reinforcement learning behavior. Here, we present our ongoing efforts to record from and manipulate neurons in the DMS during this intertemporal choice task.

Disclosures: C.E. Golden: None. **I. Trenard:** None. **C. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.14/JJ12

Topic: I.03. Decision Making

Support: R01MH139681
R01DA065418
R01MH136272
NSF CAREER Award

Title: Investigating the role of hippocampus in deliberative reward wait-time decisions

Authors: *A. PERKINS[1], R. WAKEFIELD[2], C. M. CONSTANTINOPLE[1];
[1]Ctr. for Neural Sci., [2]New York Univ., New York, NY

Abstract: Mental models are believed to undergird deliberation about potential outcomes and planning behaviors, which are important for making adaptive decisions in changing environments. Hippocampal damage is known to impair model-based planning and place memory, and hippocampus is implicated in imagining or simulating future events, which may be critical for model-based planning. We have developed a decision-making task that measures how a rat's subjective valuation of a water reward shifts across hidden states that offer different reward distributions, in which states offer high, low, or mixed amounts of water reward. Rats can choose to opt-out at any time to skip to the next trial, and modulate their wait times by block in a manner consistent with using a mental model of the task. Inactivation of dorsal hippocampus with muscimol causes rats to rapidly opt-out on a higher proportion of trials, in a manner invariant to the reward volume, block, or reward history. These rapid opt-outs are followed by bouts of anticipatory licking, implying animals mistakenly entered the opt-out port by failing to employ model-based strategies. Instead, on rapid opt-out trials, inactivated rats reverted to idiosyncratic side-biases. Recordings from dorsal hippocampus with chronically implanted Neuropixels probes have yielded recordings from hundreds of single units and local field potential during behavior. We will present our ongoing analysis of these electrophysiological recordings in the context of a task requiring decisions about how long to wait for future outcomes.

Disclosures: A. Perkins: None. **R. Wakefield:** None. **C.M. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.15/JJ13

Topic: I.03. Decision Making

Support: R01MH139681
R01DA065418
R01MH136272
NSF CAREER Award

Title: Investigating the role of ventral hippocampus in hidden state inference

Authors: *R. WAKEFIELD[1], A. PERKINS[2], C. M. CONSTANTINOPLE[1];
[1]Ctr. for Neural Sci., [2]Neurosci., New York Univ., New York, NY

Abstract: An important part of behavior is the ability to flexibly predict and adapt to the context of a given environment. These contexts may not be overtly cued, yet hidden states can be learned over time to make decisions to avoid harm or maximize reward. Hippocampus, which has been studied for episodic memory and spatial navigation, has been hypothesized to be important for understanding continuous features of the environment. In particular, the ventral hippocampus (vHPC) is known to be important for discriminating between highly similar physical contexts, and may play a role in making decisions when information about hidden states must be used. We have designed a decision-making task that measures how a rat's subjective valuation of a water reward shifts across hidden states (blocks of trials) that offer either high, low, or mixed distributions of water rewards. The high and low blocks overlap in their distributions of reward volumes, so block information is not explicitly cued and must be inferred. Experienced animals adjust their wait times across blocks. To test the role of vHPC in discriminating uncued hidden reward states, we performed muscimol inactivation of vHPC during our reward wait time task. We predict that these inactivations will lead to a collapse of wait times across blocks as animals fail to distinguish between hidden states. Additionally, it is known that the orbitofrontal cortex (OFC) is critical for value-based decision-making, and interacts with vHPC to use information about task state. Hippocampus has distinct connectivity with neocortex across the dorsal-ventral axis, with some sparse connections between vHPC and OFC. To characterize this circuitry, we performed fluorescent AAVrg injections in the ventrolateral OFC and agranular insula and then examined fluorophore expression in the vHPC. We also performed AAV1 injections in the subiculum, the major output structure of the hippocampus, to investigate disynaptic connectivity with the OFC.

Disclosures: R. Wakefield: None. **A. Perkins:** None. **C.M. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.16/JJ14

Topic: I.03. Decision Making

Support: NIH/NIDCD R01 DC020459
Klingenstein-Simons Fellowship Award in Neuroscience
NIH R01

Title: Auditory-guided inference and belief-state updating in dynamic foraging behavior

Authors: *S. BHATTACHARYA[1,2], Z. LI[3], X. PITKOW[2], R. S. WILLIAMSON[4];
[1]Carnegie Mellon Univ., PITTSBURGH, PA; [2]Neurosci. Inst., Carnegie Mellon Univ.,

Pittsburgh, PA; [3]Dept. of Ophthalmology, Stanford Univ., Palo Alto, CA; [4]Otolaryngology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Internal models of the environment constructed from sensory and reward information help animals cope with uncertainty, a core challenge of naturalistic foraging. A mouse foraging for crickets must make adaptive, auditory- and reward-guided decisions from noisy cues. Auditory cortex (ACtx) is a hub of complex auditory processing that links sounds to reward and decision processes. In contrast, prefrontal-basal ganglia circuits encode belief states that track latent environmental variables. However, how animals update these representations as they learn from ambiguous auditory cues and generalize across uncertain auditory-reward landscapes remains poorly understood. To investigate this, we developed a novel closed-loop, auditory-guided dynamic foraging task in mice, designed to probe interactions between ACtx and prefrontal-basal ganglia circuits during belief updating in inference-based decision-making. We pretrain mice on two tasks: an auditory discrimination task in which sounds signal reward location on each trial, and an inference task in which sounds are present but uninformative, so reward history alone indicates reward location within a partially observable Markov decision process (POMDP). We then test trained animals in alternating blocks in which both reward outcomes and auditory cues inform reward location, letting us dissociate purely auditory from inference-based strategies and probe their interplay during dynamic foraging. The center-out, self-paced two-alternative forced-choice (2-AFC) design gives us rich kinematic and behavioral-state measurements that reveal individual strategies and embodied action plans. In the purely auditory task, mice learn to associate auditory cues with reward locations and exhibit within-trial signatures of sensory evidence accumulation (confidence, bias, speed-accuracy tradeoffs) in their movement trajectories. Using inverse rational control (IRC), we estimate each animal's internal model of the task environment (reward and switching probabilities) and track how it evolves with learning in the inference task. In the testing stage, animals integrate auditory cues and reward history within and across trials. Body pose during the pre-stimulus hold period predicts upcoming choice in the purely inference and auditory-inference blocks, but not in purely auditory sessions, indicating an embodied preparatory signal and flexible evidence integration across multiple timescales. In ongoing experiments, we directly compare model-based and model-free learning driven by auditory cues to dissect the mechanisms of belief-state updating in ACtx and prefrontal-basal ganglia circuits.

Disclosures: S. Bhattacharya: None. **Z. Li:** None. **X. Pitkow:** None. **R.S. Williamson:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.17/JJ15

Topic: I.03. Decision Making

Support: R01MH139681
R01DA065418

R01MH136272
NSF CAREER Award
1F32MH132176

Title: A corticostriatal circuit updates subjective beliefs about latent task states

Authors: *M. L. DEMAEGD[1], D. HOCKER[1], H. GURNANI[1], M. ADLER-WACHTER[2], J. SCHINDLER[3], C. SAVIN[1], C. M. CONSTANTINOPLE[1];
[1]New York Univ., New York, NY; [2]The Scripps Res. Inst., San Diego, CA; [3]UCSD, San Diego, CA

Abstract: Beliefs about states of the world profoundly impact decision-making and learning. However, how multi-regional neural circuits represent and update beliefs is not well understood. Evidence suggests that the orbitofrontal cortex (OFC) is involved in representing beliefs when task contingencies must be inferred because they are only partially observable, and lesioning the OFC impairs animals' ability to update their inferences when state values change. Here, we sought to elucidate the role of OFC→striatal projection neurons for inference-based decision-making. We performed projection-specific recordings and perturbations from neurons in the orbitofrontal cortex (OFC) projecting to the intermediate or rostral caudate putamen (CPi/CPr) in rats performing a task with hidden reward states (low, mixed, high) represented by blocks of trials that offered different distributions of water rewards.
Stimulating OFC→CPi neurons biased rats' beliefs towards high reward states. Recordings from optogenetically-tagged OFC→CPi neurons showed that they encoded evidence for high reward states (more precisely, the *likelihood* of a reward given a high reward state), which is consistent with optogenetic stimulation biasing beliefs toward high reward states. We find that local inhibition shapes reward encoding to support categorical representations of reward volumes according to the reward state. Further, decoding from these neurons indicated that they convey the full belief distribution over states to downstream neurons.
Finally, we hypothesized that projection-specific perturbations might disrupt encoding of hidden states within the OFC via cortico-basal ganglia-thalamic loops. We used a supervised dimensionality reduction method to identify latent factors in the OFC neural activity that reflected the encoding of the hidden block, or reward volume. We found that projection-specific perturbations disrupted block representations in the OFC, but spared reward encoding.
Altogether, these findings reveal that OFC→CPi neurons encode the likelihood of encountering rewards in high reward states in their mean firing rates. Their activity causally updates beliefs, which are likely instantiated in dynamics of long-range cortico-basal ganglia-thalamic loops. This work resolves the circuit implementation of a core cognitive computation, updating subjective beliefs about abstract latent states of the environment.

Disclosures: M.L. DeMaegd: None. **D. Hocker:** None. **H. Gurnani:** None. **M. Adler-Wachter:** None. **J. Schindler:** None. **C. Savin:** None. **C.M. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

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Program #/Poster #: PSTR074.18/JJ16

Topic: I.03. Decision Making

Support: R01MH139681
R01DA065418
R01MH136272
NSF CAREER Award
K99DA062326

Title: Reward prediction errors in the dorsomedial striatum reflect contraction bias in a value-based decision making task

Authors: *I. TRENARD[1], C. E. GOLDEN[2], C. CONSTANTINOPLE[1];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: Dopamine released in the dorsomedial striatum (DMS) reflects reward prediction errors (RPEs), the difference between actual and expected reward, that are used to support reinforcement learning. However, we know very little about how working memory of reward expectations affects RPE encoding by dopamine. A hallmark of parametric working memory is contraction bias (or central tendency bias), in which a memory of a stimulus is biased toward the mean of past stimuli. Using a two-alternative forced choice task where pairs of reward values were held constant for blocks of trials, we found that as the memory of the reward values faded, RPEs were stronger. Rats chose between an offer that varied in reward magnitude and an offer that varied in reward delay. Each block began with five forced choice trials to communicate the reward values for that block to the rat and then these parameters were held constant for 20 free choice trials. We found that rats quickly learned the reward values and adjusted their choices accordingly. However, as time passed since choosing either reward, their choice probabilities were less sensitive to that reward's parameter in a manner that resembles contraction bias. For example, as time progressed since the rat chose the reward that varied in magnitude, their next choice depended less on the magnitude in that reward block, suggesting that they forgot its value. Using fiber photometry and a sensor of dopamine ($GRAB_{DA}$), we found that dopamine reflects RPEs for the chosen reward, and the RPE magnitude scales with the time since that reward was chosen, suggesting that as working memory of the reward value was subject to contraction bias, the expected value faded in memory, leading to larger RPEs. These findings relate working memory and reinforcement learning mechanisms, and show that RPEs can reveal remembered subjective values. Whether RPEs with and without contraction bias are equally used for learning is unclear. Previous work from our lab suggests that cholinergic interneurons (CINs) gate the effects of dopamine on plasticity in the dorsomedial striatum (DMS), requiring local acetylcholine (ACh) to dip prior to a phasic DA increase to allow changes to synaptic plasticity. Ongoing work is testing whether acetylcholine gates plasticity from RPEs and determines whether the observed dopaminergic RPEs support learning about reward values.

Disclosures: I. Trenard: None. **C.E. Golden:** None. **C. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.19/JJ17

Topic: I.03. Decision Making

Support: NIH R01MH139681
NIH R01DA065418
NIH R01MH136272
NSF CAREER Award

Title: Not all ramps are ramps: Neural representations of latent and embodied cognitive variables in orbitofrontal cortex

Authors: *E. L. CAPEK[1], M. DEMAEGD[1], S. SCHIERECK[2], A. H. WILLIAMS[2], C. M. CONSTANTINOPLE[1];
[1]Ctr. for Neural Sci., [2]New York Univ., New York, NY

Abstract: Neurons in many brain areas have been found to gradually increase their firing rates over time as animals form perceptual or value-based decisions. Such ramping activity is often interpreted as representing a latent decision variable that reflects the ongoing decision process. However, many dynamical processes can mimic neural ramping, muddying understanding of which brain areas are causally involved in decisions. Here we present evidence from neural recordings of orbitofrontal cortex (OFC) in rats performing a temporal wagering task. We demonstrate two separate classes of ramping dynamics in neurons whose firing rates either increase or decrease over time as rats decide whether to opt-out of a trial. OFC inactivation during the deliberation/wait period made rats' wait times longer and less sensitive to the reward offer, indicating a causal contribution to opt-out decisions. However, neurons whose trial-averaged firing rates gradually decrease over time appear to reflect sensorimotor signals, and are tightly time-locked to anticipatory licking in the reward port, which decreases over time. While the anticipatory licking can be interpreted as an embodied reflection of the underlying decision process, OFC dynamics that reflect the licking behavior are likely not directly involved in the latent decision process. Our results underscore the importance of causal interventions and ruling out confounding variables, including sensorimotor signals related to embodied cognition, when interpreting neural dynamics as reflecting cognitive processes.

Disclosures: E.L. Capek: None. **M. DeMaegd:** None. **S. Schiereck:** None. **A.H. Williams:** None. **C.M. Constantinople:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.20/JJ18

Topic: I.03. Decision Making

Support: MH124858

Title: Striatal acetylcholine enables latent-state creation during reversal learning: Part 1 Mouse Behavior & Physiology

Authors: D. LOWES[1], D. UREY[1], S. FERNANDEZ[2], I. AITSAHALIA[1], S. ENNIS[1], M. A. PRADO[3], K. IIGAYA[1], *C. KELLENDONK[1];
[1]Columbia Univ., New York, NY; [2]Columbia Univ. NYSPI, New York, NY; [3]Robarts Res. Institute/University of Western O, London, ON, Canada

Abstract: Like dopamine, the neuromodulator acetylcholine is modulated in the striatum by reward-predicting cues and outcomes. While most evidence points to dopamine acting as a prediction error in reinforcement learning, the computational role of striatal acetylcholine remains unclear. Here, we manipulated dorsomedial striatal acetylcholine levels in mice performing a reversal learning task using a combination of genetic and physiologically guided optogenetic methods. We found that phasic acetylcholine during non-rewarded trials is necessary and sufficient to support reversal learning. Computational modeling analysis showed that trial-by-trial acetylcholine dynamics were best explained by a reinforcement learning model in which new latent states are created when experience is poorly explained by existing states. A circuit-constrained model further suggested that acetylcholine promotes plasticity when reward omission is ambiguous, leading to a surprising prediction: making reward omission explicit should bypass the need for acetylcholine. We confirmed this in a new experiment that an auditory omission cue almost completely rescued the reversal-learning deficit caused by genetic knockdown of acetylcholine. These findings suggest that striatal acetylcholine supports reversal learning by promoting state construction in reinforcement learning. This poster will present the mouse experiments of this project. The modeling is presented in poster 2026-S-9223-SfN.

Disclosures: D. Lowes: None. **D. Urey:** None. **S. Fernandez:** None. **I. Aitsahalia:** None. **S. Ennis:** None. **M.A. Prado:** None. **K. Iigaya:** None. **C. Kellendonk:** None.

Poster

PSTR074: The Neural Mechanisms of Adaptive and Maladaptive Choice

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR074.21/JJ19

Topic: I.03. Decision Making

Title: Striatal acetylcholine enables latent-state creation during reversal learning: Part 2 Theory

Authors: D. UREY[1], D. LOWES[2], I. AITSAHALIA[1], M. A. PRADO[3], C. KELLENDONK[1], *K. IIGAYA[1];
[2]Dept. of Psychiatry, [1]Columbia Univ., New York, NY; [3]Robarts Res. Institute/University of Western O, London, ON, Canada

Abstract: Like dopamine, the neuromodulator acetylcholine is modulated in the striatum by reward-predicting cues and outcomes. While most evidence points to dopamine acting as a prediction error in reinforcement learning, the computational role of striatal acetylcholine remains unclear. Here, we manipulated dorsomedial striatal acetylcholine levels in mice performing a reversal learning task using a combination of genetic and physiologically guided optogenetic methods. We found that phasic acetylcholine during non-rewarded trials is necessary and sufficient to support reversal learning. Computational modeling analysis showed that trial-by-trial acetylcholine dynamics were best explained by a reinforcement learning model in which new latent states are created when experience is poorly explained by existing states. A circuit-constrained model further suggested that acetylcholine promotes plasticity when reward omission is ambiguous, leading to a surprising prediction: making reward omission explicit should bypass the need for acetylcholine. We confirmed this in a new experiment that an auditory omission cue almost completely rescued the reversal-learning deficit caused by genetic knockdown of acetylcholine. These findings suggest that striatal acetylcholine supports reversal learning by promoting state construction in reinforcement learning. This poster will present the theoretical part of this project.

Disclosures: D. Urey: None. **D. Lowes:** None. **I. Aitsahalia:** None. **M.A. Prado:** None. **C. Kellendonk:** None. **K. Iigaya:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.01/JJ20

Topic: H.03. Motivation

Support: KAKENHI 24591735
KAKENHI 22K07336
KAKENHI 18K07401
KAKENHI 15K01837,
KAKENHI 22K07608
KAKENHI 19K08332
KAKENHI 16K16648
KAKENHI 23K24074
KAKENHI 19H03410
Ishibashi Foundation

Title: Female mice form visual male preference hierarchies that predict selective dopamine responses in the nucleus accumbens

Authors: *Y. N. OHNISHI[1], Y. KAWAHARA[2], Y. H. OHNISHI[2], A. NISHI[2];
[2]Dept. of Pharmacol., [1]Kurume Univ. Sch. of Med., Kurume, Japan

Abstract: Social preference is often studied as a pairwise choice between two stimuli, yet natural social behavior frequently requires animals to evaluate multiple candidates simultaneously. Here, we developed a four-choice male-preference test in female mice to examine whether females form structured preference behavior toward multiple male stimuli. A female subject was placed in a 42 × 42 cm arena containing four corner cages, each housing a different male, and interaction time around each male was quantified.C57BL/6N female mice did not distribute investigation uniformly across males. Instead, they formed within-quartet male preference hierarchies, quantified by Top1-Top4 interaction contrast, bubble-based rank summaries, and leave-one-out hierarchy slope analyses. These measures revealed partially shared male rank structures across females, although hierarchy strength varied across quartets and individuals. Visual access contributed to this hierarchy expression: curtain-based visual occlusion disrupted structured male preference behavior, whereas visual access supported rank-based investigation patterns.We next asked whether these behavioral hierarchies predicted mesolimbic dopamine responses. Extracellular dopamine in the nucleus accumbens was measured using in vivo microdialysis coupled with HPLC-ECD during repeated exposure to behaviorally defined attractive and unattractive males. During the first exposure, both attractive and unattractive males elicited increased dopamine release in the nucleus accumbens, consistent with a response to novel male social stimuli. During the second exposure, however, dopamine release remained elevated in response to attractive males, whereas unattractive males failed to evoke a comparable dopamine response. Thus, female-defined male preference ranks predicted selective dopamine responses in the nucleus accumbens after repeated male exposure.These results suggest that female mice evaluate male stimuli through a visually supported, rank-based preference process rather than simple uniform investigation. The dopamine findings further suggest that nucleus accumbens dopamine responses may reflect both novelty and the behavioral value of male social stimuli, rather than male presence alone. Together, our findings provide a behavioral and neurochemical framework for studying how male-derived social cues are transformed into structured social preference behavior.

Disclosures: Y.N. Ohnishi: None. **Y. Kawahara:** None. **Y.H. Ohnishi:** None. **A. Nishi:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.02/JJ21

Topic: H.03. Motivation

Support: R01MH139895
McKnight Neuroscience Award
Klingenstein Foundation
SFARI

Title: Semi-supervised orthogonal non-negative matrix factorization identifies neural circuit features contributing to social behavior.

Authors: *Y. LU[1], E. ILLESCAS-HUERTA[3], R. IWATA[4], C. MARAIS[4], M. CUM[2], T. HEEPS[4], S. SAXENA[1], N. PADILLA-COREANO[4];
[1]Biomed. Engin., [2]Neurosci., Yale Univ., New Haven, CT; [3]Cell Physiol. Inst., [4]Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Social hierarchies are organizational principles that stem from collective experiences and shape group dynamics to minimize conflict and resource expenditure while maximizing reward acquisition. While studies have investigated how neural features and brain regions contribute to competitive outcomes and social dominance, the neural circuits that govern social competition remain poorly understood, particularly how the circuits encoding competitiveness differ from those encoding social outcomes.
To explore social neural circuits, we recorded local field potentials (LFP) from the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), lateral hypothalamus (LH), mediodorsal thalamus (MD), and ventral hippocampus (vHPC) of mice during social competition for reward, then calculated the power, coherence (Coh), and Granger causality (GC) as the LFP features. Next, we trained a semi-supervised model using discriminative factor analysis to identify the network states embedded within the feature array that predict outcome and competitiveness, and those common in both. The networks are initialized as selected components of a non-negative matrix factorization (NMF) of the average LFP features during social competition activity, with one component assigned to predict each social label, and another influencing the prediction of both labels. Semi-supervised training discovers networks that are both representative and predictive of target social activity. Standard NMFs have high degrees of freedom, as there exist multiple matrices that can reconstruct the input array, while orthogonal NMFs constrain the system to a more identifiable set of solutions. To balance solution uniqueness, retaining feature reconstruction, and social-activity prediction, an orthogonality constraint is applied to the model's training loss.
To test our model's generalizability to other social behavior categories, we repeated this setup with mice undergoing social cooperation tasks and computing LFP features from mPFC, MD, LH, BLA, nucleus accumbens (NAc), and inferior colliculus (IC), and trained our semi-supervised model to distinguish prosocial from selfish behaviors. The LFP features were recorded in mice undergoing social cooperation tasks, in which they may choose between button presses that give them rewards (selfish) or both (prosocial), while alone or in the presence of other mice. The semi-supervised training setup was then reiterated with new hyperparameters optimized for identifying the novel social labels from the neural networks discovered from the ONMF.

Disclosures: Y. Lu: None. **E. Illescas-Huerta:** None. **R. Iwata:** None. **C. Marais:** None. **M. Cum:** None. **T. Heeps:** None. **S. Saxena:** None. **N. Padilla-Coreano:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.03/JJ22

Topic: H.03. Motivation

Support: McKnight Foundation
Klingenstein-Simons Neuroscience Fellowship

Title: Social context-dependent dopamine dynamics in the medial prefrontal cortex and nucleus accumbens core during social interactions in mice

Authors: *A. LI[1,2], N. JIMENEZ[3], C. YE[2], M. CUM[2], S. SMITH[2], E. ILLESCAS-HUERTA[3], M. PONDER[2], S. DEHAUT[2], N. PADILLA-COREANO[2];
[1]Electrical and Computer Engin., Rice Univ., Saint Augustine, FL; [2]Neurosci., [3]Univ. of Florida, Gainesville, FL

Abstract: Dopamine (DA), a modulatory neurotransmitter, plays a critical role in motivated behaviors and reward responses. Because social interactions can be rewarding, DA has been implicated in social behavior and social decision-making (Krach et al., 2010). Recent work shows that nucleus accumbens core (NAcc) DA encodes social novelty, motivation, and valence across diverse behaviors (Dai et al., 2022); however, its role during interactions with long-term familiar partners in established social hierarchies remains unclear. The medial prefrontal cortex (mPFC) is critical for social decision-making and social rank processing, yet the role of mPFC DA signaling in social behavior remains less defined. Emerging evidence suggests that mPFC DA responds to stimulus valence and novelty (Ellwood et al., 2017; Melugin et al., 2024). However, little is known about the circuit-specific roles of DA dynamics in social interactions. To address these gaps, we measured real-time DA signaling in NAcc and mPFC while examining familiarity, hierarchy, and competition. Male C57 mice were injected with AAV-dLight1.3b and implanted with optical fibers targeting NAcc or mPFC. DA was recorded in vivo using fiber photometry, and behavior was analyzed with hand scoring and pose tracking.
Both NAcc and mPFC DA signaled social novelty during stranger encounters, with DA levels decreasing across repeated exposures and increasing when animals encountered a new novel mouse. However, during interactions with different social agents — novel, short-term familiar (10-minute prior exposure), and long-term familiar (cagemate) — we found no difference between responses to cagemates and novel agents, suggesting that DA signals more than social novelty alone. During social defeat bouts with a CD-1 aggressor, NAcc and mPFC DA show opposing DA dynamics. In a trial-based social competition task, NAcc DA responses to signal tones were greater during win than lose trials, while mPFC DA responded primarily to reward delivery. NAcc DA was also modulated by trial history, and subject-initiated competitions were associated with higher DA activity than agent-initiated competitions. Our findings suggest that NAcc and mPFC DA play distinct but complementary roles in social behavior. NAcc DA tracks socially salient features including valence, motivation, trial history, and agency during competition, whereas mPFC DA varies across social contexts. These results indicate that DA signaling during social behavior reflects current interaction structure and recent social experience.

Disclosures: A. Li: None. **N. Jimenez:** None. **C. Ye:** None. **M. Cum:** None. **S. Smith:** None. **E. Illescas-Huerta:** None. **M. Ponder:** None. **S. Dehaut:** None. **N. Padilla-Coreano:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.04/JJ23

Topic: H.03. Motivation

Support: The Peter & Carmen Lucia Buck (PCLB) Foundation Grant
Institute for Brain and Cognitive Sciences (IBAC) Research Supply Grant

Title: A novel non-food based paradigm for assessing dominance in female rats

Authors: *B. PIERRE PHILIPPE[1], G. LAURETANO[2], E. SHECTER[3], E. J. MARKUS[3];
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Abstract: The water maze is traditionally used to assess spatial learning in rodents. However, the present study evaluated a modified water maze designed to assess competitive interactions between rats. Limiting escape access to a single platform creates a socially competitive environment under aversive conditions without food as a motivator. We further examined the stability of these behaviors across time and competitive paradigms. Subjects were 10 female F344 rats, 3 months old at start of training. Rats were pair-housed with each possible partner for at least 24 hours before testing. Two rats were released simultaneously into a circular pool containing a platform that could accommodate only one animal at a time. Dominance score was based on platform possession across three time points during each trial. Each rat competed against all nine partners once daily for 8 consecutive days. Approximately 1 yr later, the same cohort completed follow-up testing following the same procedure. Additional food tower and tube competition tasks assessed whether dominance generalized across contexts. The competitive water maze produced reliable and consistent behavioral patterns across repeated testing sessions. Pearson correlation analyses revealed significant positive correlations across consecutive testing days in the initial water maze ($r = 0.88$, $p < 0.01$) and the follow-up water maze ($r = 0.86$, $p < 0.01$), indicating stable individual performance. Dominance rankings from the initial and follow-up water maze were significantly positively correlated nearly one year later ($r = 0.73$, $p = 0.02$), demonstrating long-term behavioral stability. In contrast, cross-task correlations between the water maze, tower competition, and tube competition tasks were weak and non-significant, suggesting that different competitive paradigms may assess distinct motivational or behavioral components of social hierarchy. Repeated measures ANOVA revealed that competitive interactions in the water maze declined across repeated encounters, indicating that animals established social relationships that reduced conflict over time. These findings support the use of a modified Morris water maze as a paradigm for examining competitive social behavior and long-term social hierarchy formation in rodents.

Disclosures: B. Pierre Philippe: None. **G. Lauretano:** None. **E. Shecter:** None. **E.J. Markus:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.05/JJ24

Topic: H.03. Motivation

Title: A Novel Water Platform Test Reveals Complex Social Hierarchies in Male and Female Mice

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Abstract: Social hierarchy is an evolutionarily conserved phenomenon that profoundly influences behavior, resource access, and health. However, the neural mechanisms underlying social dominance remain poorly understood, and current behavioral assays are limited. Using a novel platform test combined with region-specific neural activation analyses in male and female mice, we identified a broad spectrum of social hierarchies based on platform occupancy time, revealing greater complexity than previously reported and increased hierarchy stability in females. Behavioral measures of motivation showed a reduction in platform acquisition attempts across testing days, along with rank-dependent differences in co-occupancy behavior that were primarily observed among lower-ranked individuals. Social rank was not associated with medial prefrontal cortex (mPFC) activation but was positively correlated with lateral habenula (LHb) activation. Social dominance was further amplified in group settings compared to pairwise interactions, with similar patterns of motivated behavior and co-occupancy across ranks. Consistent with pairwise testing, mPFC activation was not correlated with rank in group contexts, whereas LHb activation was again positively correlated with rank. To examine the sensitivity of hierarchical behavior to pharmacological modulation, mice were exposed to acute nicotine vapor and reassessed. Nicotine selectively reduced social dominance behavior and rank in females, but not males, while maintaining the positive association between LHb activation and rank. Collectively, these findings highlight the complexity of social hierarchies across sexes and identify the LHb as a neural correlate of social dominance, advancing understanding of the neurobiological mechanisms underlying social hierarchy.

Disclosures: S.E. Mott: None. **A. Saha:** None. **M.A. Herman:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Topic: H.03. Motivation

Support: NIH R21MH129989
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CURE SAP#4100085747

Title: Social motivation and consumption of social rewards differentially engage projection-specific and global prefrontal neural activity

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Abstract: Strong social relationships form the cornerstone of a healthy life; conversely, disruptions in social motivation are debilitating hallmarks of psychiatric conditions, including Autism Spectrum Disorder and schizophrenia. Despite its clinical importance, the precise neural architecture driving the motivation for social interaction remains incompletely characterized. The medial prefrontal cortex (mPFC) is a critical hub orchestrating decision-making and motivated behavior via distinct downstream projections, and its global activity is known to modulate sociability and preference for social novelty. However, how specific, projection-defined mPFC populations contribute to sustaining social motivation remains unknown. Here, we employed an operant social self-administration paradigm to quantify social motivation in male and female mice. Using fiber photometry to record calcium dynamics, we monitored bulk mPFC activity during social self-administration, and further dissected circuit specificity by recording exclusively from mPFC neurons projecting to the paraventricular nucleus of the thalamus. We reveal that general mPFC population activity surges immediately following an operant nosepoke for a social stimulus, but decreases upon the initiation of social contact. Together, these findings identify a precise temporal divergence in prefrontal signaling, underscoring the distinct roles of mPFC circuits in the pursuit versus the consumption of social rewards.

Disclosures: V. Migovich: None. **W. Gao:** None. **R.A. España:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.07/KK2

Topic: H.03. Motivation

Support: T32 5T32NS041228
Robin L Smith Fellowship
Charles BG Murphy Fund

Title: Stable juvenile play archetypes characterize individual differences in rough-and-tumble play in rats

Authors: *T. M. REICHARD[1], S. W. LI[2], R. A. CAUCHON[2], H. W. KIETZMAN[2], J. R. TAYLOR[3];
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Abstract: Social behavior in animals varies tremendously in both naturalistic and laboratory environments and shapes how animals respond to others. These individual differences emerge across species and are present even among genetically identical organisms. In rats, some individuals reliably release a trapped conspecific whereas others do not, and this behavior is shaped by developmental social experience. Rough-and-tumble play (RTP) is the dominant form of juvenile social behavior in rats and is required for the normal development of adult social competence. Prior work has largely focused on play deprivation or isolation paradigms, rather than asking whether natural variation in juvenile play style predicts adult phenotype. We hypothesized that juvenile play is organized into stable individual archetypes that are prospectively linked to adult prosociality.
We characterized peri-pubertal play behavior (P53-67) in 24 Wistar rats (16F, 8M) across four 10-min dyadic play sessions, half preceded by 6 hours of social isolation to increase play motivation. From hand-scored BORIS ethograms, we derived a 22-feature profile for each rat, including measures of initiation, reciprocity, behavioral repertoire diversity, and dyadic event coupling. We performed a principal-convex-hull archetype analysis that identified three reproducible player archetypes: A1 - fast initiators with narrow behavioral repertoires with low partner coupling (mixed sex), A2 - recipients of play who quickly disengage (predominantly female), and A3 - reciprocal, typical RTP play (exclusively male, 4/8 males). Archetype assignment was trait-like and stable - 22 of 24 rats retained their dominant archetype across both group-housed and isolated conditions. Six hours of isolation produced a male-specific within-session rebound in play ($p=0.014$) without shifting archetype identity.
We are replicating this framework in Long-Evans rats to test whether player archetypes generalize across strains and are evaluating adult prosocial and decision-making tasks within-subjects to determine whether juvenile archetype predicts later behavior. These findings establish a quantitative framework for characterizing individual and strain differences in juvenile play and for testing whether developmental social trajectories are fixed or flexible. In future studies, we will test whether oxytocin-sensitive anterior cingulate cortex to basolateral amygdala and related corticolimbic circuits organize juvenile play archetypes and their links to adult prosocial behavior.

Disclosures: T.M. Reichard: None. **S.W. Li:** None. **R.A. Cauchon:** None. **H.W. Kietzman:** None. **J.R. Taylor:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.08/KK3

Topic: I.06. Social Cognition

Title: Microhabits in Social Foraging: Mice Minimize Complexity Costs Through Habitual Dwell Time Patterns

Authors: *E. TURE, D. KVITSIANI, E. DEMIR;
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Abstract: Every social choice carries an opportunity cost: for a thirsty mouse, time spent with a partner is time away from water. Adaptive social foraging therefore requires continuous arbitration between social value, physiological need, and reward uncertainty. However, sustaining this balance can be computationally demanding. We hypothesized that mice manage this trade-off by shifting between two control states: a flexible information-sampling state, in which partner value, opportunity cost, and reward uncertainty are updated from current cues and recent outcomes, and a history-dominated microhabit state, defined as short-range reuse of recent stay/leave patterns. To test this, we used a custom-engineered social-foraging platform in which thirsty male mice shuttle between a water patch and a social carousel containing female conspecifics from multiple strains or empty cages. A variable gate delay imposed an access cost to the social patch; after entry, mice freely determined how long to interact before returning to collect water. Using linear mixed-effects model, we predicted current dwell time from partner identity, entry cost, water outcome, and social/dwell-history terms extending up to three trials back. Mice formed stable partner preferences, but current behavior was not determined by partner identity alone: long dwell times tended to recur over subsequent trials, revealing short-range history dependence consistent with microhabit formation.We next tested whether reward context changed the relative influence of current value versus behavioral history. When water magnitude increased five-fold after visits to the preferred ICR cue, mean water reward rate increased and the influence of recent dwell history strengthened, consistent with stronger microhabit control. In contrast, when water outcome varied randomly across trials—omission, regular reward, or double reward—while preserving mean reward rate, microhabit-like history dependence was strongest during repeated regular-reward sequences. Unexpected omissions or reward increases disrupted these history effects and shifted behavior toward flexible updating.Together, these findings suggest that microhabits act as adaptive shortcuts for social time allocation when reward conditions are stable. By reusing recent dwell-time patterns, mice can stabilize social foraging without recomputing partner value on every trial. Yet this efficiency may become maladaptive when recent history begins to dominate over current reward evidence, causing flexible social foraging to harden into rigid or perseverative behavior.

Disclosures: E. Ture: None. **D. Kvitsiani:** None. **E. Demir:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.09/KK4

Topic: H.03. Motivation

Support: NIH Grant 1R21MH136446-01A1
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Title: The Anterior BNST Is Required for Novelty-Driven Social Interaction

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Abstract: Social novelty preference—the tendency to interact more with unfamiliar than familiar conspecifics—is conserved across species and disrupted in disorders such as autism spectrum disorder, schizophrenia, and social anxiety. While the hippocampus and related circuits are known to encode social recognition memory, the mechanisms that translate familiarity signals into behavioral differences remain unclear. Here, we show that male mice exhibit a robust preference for engaging with unfamiliar over familiar conspecifics. Using c-Fos labeling, RNAscope, immunohistochemistry, and fiber photometry, we found that inhibitory and DRD1 expressing neurons in the dorsal subdivision of the anterior bed nucleus of the stria terminalis (BNSTa) are broadly activated during social and novel-object interaction. However, chemogenetic inhibition of the BNSTa selectively suppressed interaction with unfamiliar conspecifics while leaving familiar and novel-object interactions unaffected. These findings identify the BNSTa as a critical node that promotes novelty-driven social engagement, revealing a circuit mechanism for social novelty preference. Because deficits in novelty processing are central to multiple neuropsychiatric disorders, our results highlight the BNST as a potential locus of dysfunction linking social recognition to behavior.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.10/KK5

Topic: I.06. Social Cognition

Support: NIMH R01MH139795
NIMH R01MH123768

Title: A novel and potential sex-specific role for basolateral amygdala parvalbumin interneurons in mouse social behaviors

Authors: *B. HARDIN[1], A. L. BUNCE[3], A. FARTHING[4], N. E. BAUMGARTNER[5], E. K. LUCAS[2];
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Biomed. Sci., North Carolina State Univ., Raleigh, NC; [5]Psychiatry & Behavioral Neurobio., Brainbow Prints, Birmingham, AL

Abstract: Social behaviors represent fundamental processes across species and are dysregulated in several psychiatric and neurodevelopmental conditions. Oxytocin, a well-studied nonapeptide produced in the paraventricular and supraoptic nuclei of the hypothalamus, is a potent regulator of social behaviors such as pair bonding and social recognition. Our single nucleus RNA sequencing data demonstrate expression of the oxytocin receptor in parvalbumin inhibitory interneurons (PVIs) of the basolateral amygdala (BLA). We hypothesize that BLA PVIs are thus involved in social behaviors and may modulate these processes as the result of activation of the oxytocin receptor. To first assess the activity pattern of BLA PVIs during social interactions, we performed *in-vivo* calcium imaging of BLA PVIs during the three-chamber social interaction test in adult ($\geq$ 3 months of age) male and female PV-IRES-Cre. Our results reveal robust engagement of BLA PVIs during interactions with an age-matched, sex-matched conspecific compared to a novel object in both sexes. Further analysis revealed that this robust engagement was greatest for the first social interaction, suggesting BLA PVIs are selectively involved in novel social interactions. To test the hypothesis that increasing BLA PVI activity would enhance sociability, we chemogenetically activated BLA PVIs using a Cre-dependent excitatory Designer Receptor Exclusively Activated by Designer Drugs (AAV8-DIO-eDREADD-mCherry) in adult PV-IRES-Cre male and female mice. Paradoxically, continuous PVI activation during the social interaction task increased latency to interact with the novel conspecific in both sexes and decreased sociability selectively in females. These data suggest that sex differences may exist in PVI function and the timing of PVI activity is likely critical for normal social behaviors. To assess sex differences in BLA PVI function, we performed patch-clamp recordings in acute brain slices from PV-IRES-Cre x Ai9-TdTomato mice. We observed increased excitability in females compared to males as evidenced by increased action potential frequency and decreased rheobase current. Together, our current data reveal a novel and potential sex-specific role for BLA PVIs in modulating social behaviors. Future studies employing a transgenic animal model will better examine the causal link between activation of the oxytocin receptor in BLA PVIs and sociability. The observed sex differences in BLA PVI function may contribute to sex differences in susceptibility to neuropsychiatric and neurodevelopmental conditions characterized by social dysfunction.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.11/KK6

Topic: I.06. Social Cognition

Title: Neuroanatomical and functional characterization of the mouse Indusium Griseum

Authors: H. VÉLEZ GONZÁLEZ, P. GIMENEZ GOMEZ, *F. LEROY;
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Abstract: The indusium griseum (IG) is a brain structure composed of two narrow longitudinal bilateral strips that run above the corpus callosum (CC) in its rostrocaudal length. The IG is critical during development for the formation of the CC its function in adult mice remains unknown. Because IG is connected with the hippocampus, cingulate cortex, and septal region—key hub regions implicated in social behavior—we hypothesized that it may contribute to social discrimination. To test this, we used Cre-expressing mice of both sexes to selectively target IG. First, we employed anterograde and retrograde viral tracing to map IG connectivity and found that IG receives primarily inputs from the anterior cingulate, motor, piriform, entorhinal, and retrosplenial cortices, while projecting mainly to the septohippocampal nucleus and to a lesser extend to the fasciola cinerea. Then, used chemogenetic to assess the behavioral impact of silencing IG neurons during locomotion, anxiety, feeding, olfactory and social behaviors test. We observed that IG inhibition blocked social novelty preference while leaving locomotion, anxiety, feeding. and olfaction intact. These results align with our fiberphotometry recordings, suggesting that IG neurons are preferentially engaged by social cues. Overall, our results show that IG integrates social cues from cortical signals to support social novelty preference in the mouse.

Disclosures: H. Vélez González: None. **P. Gimenez Gomez:** None. **F. Leroy:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

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Program #/Poster #: PSTR075.12/KK7

Topic: I.06. Social Cognition

Title: Medial Prefrontal Cortex Represents Group and Individual Identity during Group Fusion in a Rat Society

Authors: *Y. PAN[1,2], M. PROSKURIN[2], E. KULESHOVA[2], D. SCHAUDER[3], S. ABDULKAREEM[4], D. G. TERVO[2];
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Abstract: Rats live and make decisions in complex societies that are structured by emergent dominance hierarchies and group and individual affiliations. However, such societal structures, the behaviors that generate them and the neural bases of these behaviors are understudied. A reason for this is that studying them requires continuously monitoring natural behavior and physiology in freely interacting animals. To investigate these processes, we built "RatCity," an indoor naturalistic environment, and then developed a group fusion paradigm, which requires rats in pre-established groups to renegotiate their social relationships when merged into a new

society.We divided an arena in two with a wall containing a lockable door and allowed two kin groups of six male rats each to establish territories on either side. We continuously recorded behavior with cameras and ultrasonic vocalizations with a microphone array for two weeks, while simultaneously recording neural activity wirelessly and longitudinally from multiple rats. After seven days of territory establishment, we opened the door joining the two compartments. Conflict-- 'fighting','chasing', 'pushing' and 'defending'--between rats rose sharply on the first day and fell by half over the next three days. The target of conflict depended on both group affiliation and the pairwise history of aggression between rats. During social encounters, prefrontal cortical activity encoded the identity and group affiliation of opponents, and population activity additionally encoded the interaction outcome. Together, these results show that prefrontal cortical neurons encode multiple features of social information during decision-making in complex societies.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

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Program #/Poster #: PSTR075.13/KK8

Topic: A.07. Development of Neural Systems

Support: NIMH Grant R56MH133628

Title: Socially Tuned Adaptive Coding in the Mouse Paralaminar Amygdala Correlates with Behavioural Discrimination

Authors: *S. KUMAR[1], L. HEIER[2], D. SIKORSKI[3], J. CORBIN[4], K. HSIAO[5];
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Abstract: The paralaminar nucleus (PL) of the amygdala, located adjacent to the basolateral amygdala, contains a population of neurons that remain immature until adolescence before rapidly differentiating into excitatory neurons. Our previous work demonstrated that this developmental program is conserved between mice and humans and revealed reciprocal connectivity between the PL, other amygdala nuclei, and secondary olfactory regions (Alderman et al., Neuron, 2024; Saxon et al., eNeuro, 2024). Despite its unique developmental trajectory and connectivity, the functional role of the PL in behavior remains poorly understood. Here, we monitored PL activity in awake behaving mice during odor exposure and social interaction. PL neurons exhibited temporally tuned responses to odor stimuli that progressively attenuated with repeated presentations, consistent with adaptive encoding of stimulus novelty. Although responses to all odor categories declined over time, social odor responses attenuated more

slowly. Across both head-fixed odor presentation and freely moving behavioural paradigms, PL activity was strongest for ethologically salient stimuli, including food and social Odors. In freely moving animals, PL activity was selectively associated with social investigation and discriminated between distinct social cues during early interactions, with this neural discrimination diminishing over subsequent encounters. Importantly, the magnitude of early neural discrimination was linearly correlated with behavioral discrimination measured across the entire session, quantified from the relative time animals spent investigating each cue. These findings suggest that PL activity encodes the initial behavioral relevance of social stimuli and is associated with subsequent social preference.
Pharmacological disinhibition abolished response attenuation while preserving temporal tuning, indicating that adaptive response decay arises from active recruitment of inhibitory circuits rather than passive sensory adaptation. Ongoing viral and optogenetic experiments are testing the hypothesis that inhibitory mechanisms regulate PL circuit maturation and behavioural function. Together, our findings identify the PL as a socially tuned adaptive filter that links novelty encoding with behaviorally relevant social cue discrimination through inhibitory gating mechanisms.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.14/KK9

Topic: I.06. Social Cognition

Support: 1R01MH130755-01A1

Title: Determining the role of local interneurons in shaping reward responses in the medial prefrontal cortex of mice

Authors: *H. BALASUBRAMANIAN[1], J. ISAAC[1], M. MURUGAN[2];
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Abstract: Affiliative social interactions are crucial to an animal's survival and have been identified to engage the cortico-limbic reward circuitry similar to food rewards. How these distinct rewarding scenarios are encoded in the brain has garnered significant attention. We previously identified that within the medial prefrontal cortex (mPFC) of mice, these rewards are represented in largely nonoverlapping ensembles. However, the contribution of the local microcircuit to shaping these reward responses is largely unknown. Here we focus on the role of the fast-spiking (FS) interneurons and their interactions with the local excitatory neurons to explain underlying reward representations in the mPFC. We performed cellular-resolution calcium imaging of FS interneurons (n=8 mice, ~300 neurons) and Vglut1^{+} excitatory neurons

(n=8 mice, ~800 neurons) as mice performed a self-paced social-nonsocial two-choice operant task. By mapping their neural encoding properties using a lasso-regularized linear kernel representation, we found that excitatory neurons are modulated by both social and sucrose rewards, leading to largely separable ensembles at the population level. In contrast, FS interneurons were strongly biased toward the social reward (Reward selectivity index FS interneurons vs excitatory neurons, KS test $p<0.005$). We additionally showed that the social reward bias in the interneurons could neither be explained by novelty of the reward nor by its presentation in a novel location. Rather, at a population level, the interneurons closely tracked the animal's entries and exits into the social reward zone during rewarded trials better than excitatory neurons (Mutual information (MI) between reward zone tracking and extracted low-dimensional neural response vector for each trial, $p<0.05$). Furthermore, to identify the causal role of the interneurons in the mPFC reward circuitry, we monitored the activity of the excitatory neurons while chemogenetically silencing the interneurons. This led to disruptions in the reward-seeking behavior (1-way ANOVA, Baseline vs Saline vs CNO, $p<0.0005$) and induced hypersynchrony in the excitatory neurons. This in turn resulted in a significant loss in the encoding of reward-related information (MI, Baseline vs CNO vs Saline, $p<0.05$).Thus, these findings suggest that FS interneurons act as modulators of signal-to-noise ratio in the mPFC microcircuit. Through structured inhibition, they sharpen the distinction between reward representations in the excitatory population, thus preserving reward-related information that promotes the animal's reward-seeking behavior.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.15/KK10

Topic: I.06. Social Cognition

Support: NIH T32 NS096050
NIH F31 MH135662

Title: Transformation of social recognition representations across the hippocampal-septal circuit

Authors: *B. DYKSTRA, C. SEVINÇ, G. BERMAN, M. MURUGAN;
Biol., Emory Univ., Atlanta, GA

Abstract: Mice differentially interact with novel and familiar conspecifics suggesting that they can recognize previously encountered individuals and use that recognition information to inform behavioral decisions. Prior work has demonstrated that inhibiting the ventral hippocampus disrupts the natural preference to investigate novel mice over familiar mice indicating that the ventral hippocampus is necessary for social recognition. Importantly, the ventral hippocampus is primarily composed of two functionally distinct subfields (the vCA1 and vCA3) and it remains

unknown whether these subfields differentially encode social recognition information. Additionally, both the vCA1 and vCA3 strongly project to the lateral septum (LS), a primarily GABAergic region in the basal forebrain. Lesioning and inhibiting the LS also disrupts social novelty preference however it remains unclear how the LS integrates and transforms social recognition input from the vCA1 and vCA3. Here we perform cellular resolution one photon calcium imaging to record endogenous activity in the vCA1, vCA3 and LS in three separate cohorts of mice. Mice then freely interact with a series of novel and familiar conspecifics while all behaviors are automatically tracked and annotated. Within the ventral hippocampus we find that a larger proportion of vCA3 neurons have a significant social preference compared to vCA1 neurons suggesting that the subfields differentially encode social recognition information. In the LS, an even greater proportion of neurons display a social preference with a strong bias for the novel conspecific over the familiar conspecific. Support vector machines trained on population-level LS activity can decode novel and familiar conspecifics but cannot decode two familiar conspecifics above chance suggesting a specific role in social novelty decoding. Decoding accuracy is highest at interaction onset and declines as novelty diminishes, tracking the behavioral expression of recognition in real time. Together, these findings reveal that social recognition signals are progressively transformed along the hippocampal-septal circuit, with the LS emerging as a key locus for social novelty discrimination.

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Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

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Program #/Poster #: PSTR075.16/KK11

Topic: H.03. Motivation

Support: NIH Grant MH133628

Title: Investigating the role of excitatory amygdala paralaminar neurons in adult mouse social behavior

Authors: *S. L. SANTIAGO[1,2,3], S. F. SORRELLS[1,2,3];
[1]Neurosci., [2]Ctr. for Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [3]Ctr. for the Neural Basis of Cognition, Carnegie Mellon Univ., Pittsburgh, PA

Abstract: The amygdala paralaminar nucleus (PL) contains up to 20% of neurons in the human amygdala, yet its function remains poorly understood. PL neurons are primarily excitatory (~80% Tbr1+) and undergo prolonged maturation extending through adolescence, an important age for social development. In mice, the PL receives input predominantly from olfactory and amygdala regions and projects reciprocally to these areas and to olfactory, reward, memory, and valence networks, positioning it well to integrate acute olfactory cues with internal state. However, the specific contribution of the adult PL to social behavior is unknown. We

hypothesized that excitatory PL neurons in the adult mouse are necessary to influence decisions and behavior in a social context. To test this, we chemogenetically silenced Vglut2+ PL neurons using an inhibitory Designer Receptor Exclusively Activated by Designer Drugs (DREADD) in 11 adult (P85-P105) Vglut2-cre mice (5 male, 6 female). In a within-subject crossover design, each animal received the DREADD agonist deschloroclozapine (DCZ) or saline before behavioral testing with a three-chamber social preference task and an open-field reciprocal social interaction task. PL targeting was confirmed histologically (n = 6 bilateral PL, 5 unilateral PL). In the three-chamber task, mice showed no preference for either chamber during habituation when treated with saline (mean pref. index=0.10, SD=0.26; N=11) or with DCZ (-0.17 ± 0.43; N=11). During the same three-chamber task, mice preferred a conspecific over an empty cage (sociability), with no marked difference in preference index when treated with saline (0.37 ± 0.37; N=11) or DCZ (0.31 ± 0.60; N=11). When given the opportunity to explore a chamber with a novel or a familiar conspecific (social novelty), mice had no strong preference for either chamber when treated with saline (-0.13 ± 0.48; N=11) or with DCZ (-0.06 ± 0.47; N=11). These data suggest that silencing adult excitatory PL neurons may not be required for social preference or investigation under these conditions. These data differ from our open-field reciprocal interaction task, where we see exploratory behavior and locomotion vary when DCZ-treated mice are in a social vs a non-social context. This work establishes a framework for studying excitatory neurons in the adult PL, where dense olfactory connectivity may support a role in linking acute olfactory cues to behavioral state.

Disclosures: S.L. Santiago: None. **S.F. Sorrells:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.17/KK12

Topic: I.06. Social Cognition

Support: IZLCZ0_206045
IZLIZ3_200297
310030_192463
3200-0-239999
Synapsis Foundation No. 2020-PI02

Title: Chemogenetic inhibition of the basolateral amygdala alters reward allocation in a rat prosocial pulling task

Authors: *R. TOMÀ[1], E. VAN DEN BURG[2], R. STOOP[2];
[1]Univ. of Lausanne/CHUV, Lausanne, Switzerland; [2]Ctr. Psychiatric Neurosci., Prilly, Lausanne, Switzerland

Abstract: The basolateral amygdala (BLA) has been implicated in reward valuation, decision-making, and social behavior. Human studies of patients with Urbach-Wiethe disease (UWD), a rare genetic condition associated with selective bilateral BLA calcification, suggest that the BLA contributes to balancing self-directed and other-directed motivation. However, causal investigations of BLA function in social effort allocation remain limited. Given the evolutionary conservation and functional expansion of the BLA across species, rodent models and in particular rats, which display rich social behavior provide an opportunity to investigate the neural mechanisms underlying these behaviors. To address this question, we developed a rat Prosocial Pulling Task adapted from previous reciprocity paradigms. Female Sprague Dawley rats (n=12) received bilateral injections of inhibitory DREADDs in the BLA and were trained to pull one platform delivering food to themselves and another platform delivering food to a conspecific housed in an adjacent compartment separated by a transparent perforated divider allowing visual, olfactory and limited tactile interactions. Following post-surgery recovery and a four week training protocol, eight animals reached stable behavioral performance and completed testing. Behavioral performance was assessed across three sessions: baseline, chemogenetic inhibition of BLA with deschloroclozapine administration, and recovery. Pulling behavior was normalized to session duration and used to calculate a self/other preference index. No baseline platform bias was observed after training (Wilcoxon signed-rank test, p=0.350). Chemogenetic inhibition of the BLA increased the self/other preference index relative to baseline (Wilcoxon signed-rank test, p=0.039), with a partial recovery observed during the recovery session (baseline vs. recovery, p=0.078). Examination of individual pulling rates suggested that this shift was associated with reduced responding directed toward the conspecific, while self-directed responding was comparatively preserved, although neither measure reached statistical significance when analyzed separately (self: p = 0.641; other: p = 0.547). These preliminary findings suggest that transient inhibition of the BLA alters the balance between self-directed and other-directed reward-seeking behavior. These results validate a translational rodent model of social reward allocation and provide a framework for future investigations of neural circuits underlying social valuation and effort allocation.

Disclosures: R. Tomà: None. **E. Van den Burg:** None. **R. Stoop:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.18/KK13

Topic: I.06. Social Cognition

Title: Neuropeptide release and disinhibition interact in the control of inter-male aggression by medial amygdala GABA neurons

Authors: *N. JANA[1], A. BALEISYTE[2], D. KIM[3], S. HAN[3], R. SCHNEGGENBURGER[1], O. KOCHUBEY[1];

[1]Lab. of Synaptic Mechanisms, EPFL, Lausanne, Switzerland; [2]The Rockefeller Univ., New York, NY; [3]Peptide Biol. Lab., The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Aggression is a fundamental social behavior, critical for the success of animal populations. The medial amygdala (MeA) is an important hub for processing social cues, and contains both glutamatergic and GABAergic projection neurons. Optogenetic stimulation of MeA-GABA neurons triggers inter-male aggression (Hong et al. 2014); however, this effect depends on the excitatory opsin variant employed (Baleisyte et al. 2022). MeA-GABA neurons project to hypothalamic nuclei including Esr1+ neurons in the VMHvl, and GABAergic neurons in the adjacent tuberal (TU) area (Jana et al., 2025, SfN abstract). TU-GABA neurons, in turn, contact VMHvl-Esr1+ neurons; the latter neurons are involved in aggression regulation (Lee et al., 2014). Here, we hypothesize that stimulation of MeA-GABA neurons under a strong optogenetic stimulation regime drives aggression via a possible interaction between disinhibition of VMHvl-Esr1+ neurons, and mobilization of neuropeptide release. $VGAT^{Cre}$ mice crossed with the CD1 strain were used in the resident-intruder assay, to ensure reliable baseline aggression. Optogenetic stimulation in the VMHvl of MeA-GABA axons expressing the slow excitatory opsin $ChR2^{H314R}$ (called ChR2 below), led to reliable stimulation of aggression, whereas stimulation with the faster Chronos and no effects. To test the role of TU-GABA mediated disinhibition, we combined optogenetic stimulation of MeA-GABA axons using ChR2, with chemogenetic inhibition of TU-GABA neurons. This significantly reduced the degree of aggression stimulation, but some amount of stimulated aggression remained. We therefore next tested whether aggression stimulation might be caused by a mobilization of neuropeptide release from MeA-GABA axons, by employing Neutral Endopeptidase targeted to large-dense core vesicles (LDCV-NEP), which suppresses neuropeptide release (Kim et al., 2024). Cre-dependent co-expression of LDCV-NEP, alongside with ChR2 in MeA-GABA neurons, led to a significant, but still incomplete block of aggression stimulation, and to qualitative changes in attack behavior. Finally, to test whether the remaining aggression stimulation in the presence of LDCV-NEP is driven by disinhibition, we combined LDCV-NEP expression with chemogenetic inhibition of TU-GABA neurons in optogenetic MeA-GABA axon stimulation experiments. This led to a near-complete absence of aggression stimulation. Our results show that a disinhibition of VMHvl neurons, originating from MeA-GABA neurons via the TU-GABA neurons, together with neuropeptide release caused by strong optogenetic activation of MeA-GABA axons, synergistically drive an immediate aggressive state.

Disclosures: N. Jana: None. **A. Baleisyte:** None. **D. Kim:** None. **S. Han:** None. **R. Schneggenburger:** None. **O. Kochubey:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.19/KK14

Topic: I.06. Social Cognition

Support: R01DA058958
R01DA058098
R00DA045795
R34DA061267
R30DA033934
Blick Scholar Fund

Title: Derepression of transposable elements in mouse prefrontal cortex disrupts synchronous neuronal ensemble activity during social interactions

Authors: *K. F. HOAG, C. SMITH, P. GOSWAMEE, P. J. HAMILTON;
Virginia Commonwealth Univ., Richmond, VA

Abstract: Social behavior is central to the health of both the individual and society. Altered social behavior occurs in many neurodevelopmental and psychiatric disorders, however, the underlying neurobiological cause of such behavioral dysfunction is not well understood. Transposable elements (TEs) are repetitive DNA sequences that comprise about half of the mammalian genome. TEs are involved in establishing *cis* regulatory genomic regions, and TE dysregulation has been implicated in multiple neurodevelopmental and psychiatric disorders, including those characterized by social deficits. Transcriptional control of brain TEs is largely mediated by KRAB zinc finger proteins (KZFPs) along with the repressive cofactor, TRIM28. Our lab has previously shown that viral delivery of a synthetic TRIM28^{VPR} construct, which activates TE transcription in the medial prefrontal cortex (mPFC) of male and female C57/BL6J mice, impedes immune gene expression and impairs social behavior. However, the neuronal microcircuit functional consequences of this TRIM28-mediated TE dysregulation remains unknown. Here, we used two synthetic TRIM28 variants to differentially control mPFC TE transcription: TRIM28^{WT} (endogenous TRIM28) and TRIM28^{VPR} (endogenous TRIM28 with synthetic activator domain VPR), as well as a control mCherry. These constructs were packaged in AAV8 and stereotaxically delivered bi-laterally to the mPFC of male and female mice alongside AAV1-GCaMP6f. Following viral delivery and GRIN lens implant surgery, calcium events were recorded in awake and behaving mice during the Three Chamber Social Test and Novel Object Recognition assays. In TRIM28^{VPR} mice, we observed asynchronous activity in the neurons of the mPFC during social interactions and object recognition. Conversely, TRIM28^{WT} mice exhibited synchronous mPFC neuronal activity during both social interactions and object recognition. Our studies suggest that the TRIM28-mediated transcriptional control of TEs in the neurons of the mPFC contribute to the organization of mPFC neuronal activity which is necessary for prosocial behaviors. This work points to the circumstances in which brain TE transcripts are released as potentially contributing to the social cognition deficits that define many brain disorders.

Disclosures: K.F. Hoag: None. **C. Smith:** None. **P. Goswamee:** None. **P.J. Hamilton:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.20/KK15

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Pharmacological Activation of alpha7 nAChRs Improved Autistic-related Behaviors in BTBR Mouse Model

Authors: *S. ALSHARARI[1], M. DAMAJ[2], M. A. ALSHAMMARI[3];
[1]King Saud Univ., Riyadh, Saudi Arabia; [2]Dept. of Pharmacol. & Toxicology, Virginia Commonwealth Univ., Richmond, VA; [3]Pharmacol. and Toxicology, Col. of Pharmacy, King Saud Univ., Riyadh, Saudi Arabia

Abstract: Abstract.Nicotinic acetylcholine receptors (nAChRs), particularly the α7 nAChR, are implicated in the pathophysiology of CNS disorders, including Autism Spectrum Disorder (ASD). The involvement of the brain nicotinic neurotransmission system plays a crucial role in regulating autism-related behavioral features. This study examined the behavioral effects of pharmacologically targeted nAChRs using selective α7 nAChR ligands, PNU-282987 (3 and 10 mg/kg, s.c.), a selective α7 nAChR agonist, and methyllycaconitine (MLA), the selective α7 nAChR antagonist, in a BTBR T^+ $Itpr3^{tf}$/J mouse model of autism. We conducted a panel of behavioral tests relating to autistic behaviors, including sociability and repetitive behaviors in C57B and BTBR T^+ $Itpr3^{tf}$/J mice. The behavioral tests included the three-chamber social interaction, self-grooming, marble burying, locomotor activity, and rota-rod tests. Activation of the α7 nAChRs with PNU-282987 significantly improved the sociability, repetitive behaviors, and motor coordination on the rota-rod tests in BTBR T^+ $Itpr3^{tf}$/J mice and a significant effect was observed at 10 mg/kg. Moreover, the involvement of the α7 nAChR in these tests was confirmed by antagonizing the effects of 10 mg/kg PNU-282987-treated BTBR T^+ $Itpr3^{tf}$/J mice using MLA. Moreover, PNU-282987 did not show any significant differences at all examined doses on the locomotor activity test. In this study, we showed, for the first time, the effect of selective α7 nAChR ligands in the modulation of sociability and repetitive behaviors in BTBR T^+ $Itpr3^{tf}$/J mice. This study elucidates the potential therapeutic values of a pharmacological intervention targeting α7nAChRs for ASD therapy. **Keywords**: Autism, Nicotine, sociability, repetitive, nAChRs, PNU-282987.

Disclosures: S. AlSharari: None. **M. Damaj:** None. **M.A. Alshammari:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.21/KK16

Topic: H.03. Motivation

Support: NIMH R01 MH131807

Title: Vasopressin 1a receptor-expressing neurons in the mouse ventral tegmental area are predominantly GABAergic.

Authors: *M. SADEGHI ALIABADI[1,2], N. HINDS[3,5], H. CHOHAN[4], T. GOOD[3,5], B. D. ROOD[5,3];
[1]Rowan Univ., Stratford, NJ; [2]Neurosci., Rowan-Virtua Translational Biomed. Engin. and Sci., Stratford, NJ; [3]Neurosci., Rowan-Virtua Sch. of Osteo. Med., Stratford, NJ; [4]Rowan-Virtua Sch. of Osteo. Med., Winslow Township, NJ; [5]Neurosci., Rowan-Virtua Sch. of Translational Biomed. Engin. and Sci., Stratford, NJ

Abstract: Social behavior is integral to survival and well-being, regulated by dynamic interactions between the social behavior network and the mesocorticolimbic reward pathway, which together comprise the social decision-making network. Despite substantial progress in characterizing social neuronal circuits, the neuronal mechanisms underlying social motivation remain poorly understood. Vasopressin (Avp), a neuropeptide produced in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA), regulates both prosocial and antisocial behaviors. Tract-tracing studies have previously delineated Avp-immunoreactive projections from the BNST and MeA to the ventral tegmental area (VTA). Dopaminergic VTA neurons are well-established mediators of nonsocial reward processing and have been shown to govern social reinforcement behaviors, including social attachment and mating. To further interrogate the role of the VTA in social behavior, we examined neuronal activation patterns during social interaction and characterized the neurochemical phenotype of Avpr1a-expressing neurons within the VTA. Brains were collected 90 minutes following a 20-minute social interaction between a male and either an ovariectomized or hormonally primed ovariectomized female, and processed immunohistochemically for c-Fos to index neuronal activation. Males exposed to hormonally primed females exhibited significantly greater Fos-immunoreactive cell density in the VTA relative to vehicle-treated controls, indicating enhanced recruitment of VTA circuitry by a reproductively receptive partner and suggesting that VTA activity is modulated by cues reflecting the motivational or hormonal state of a conspecific. Given that dopaminergic and Avpr1a-expressing neurons within the heterogeneous VTA have been implicated in overlapping social behavioral repertoires, it is possible that these populations functionally interact. To characterize the neurochemical identity of VTA Avpr1a neurons, multiplex fluorescent RNAscope in situ hybridization was conducted in adult C57BL/6J mice with probes targeting Avpr1a, tyrosine hydroxylase (TH), vesicular glutamate transporter (vGlut2), and vesicular GABA transporter (vGAT). Preliminary findings reveal that Avpr1a-expressing neurons within the VTA are predominantly GABAergic, while also encompassing a dopaminergic subpopulation, collectively demonstrating that VTA Avpr1a neurons constitute a neurochemically heterogeneous population.

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

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.22/KK17

Topic: H.03. Motivation

Support: Arnold and Mabel Beckman Foundation

Title: Oxytocin receptor signaling in the ventral tegmental area, nucleus accumbens, or lateral septum mediates social reward in rats

Authors: *J. STALL[1], K.-C. LEONG[2];
[1]Dept. of Neurosci., [2]Dept. of Psychology, Trinity Univ., San Antonio, TX

Abstract: Investigating the neural mechanisms underlying social reward is important not only to further the current understanding of what drives social interaction, but also for informing potential therapeutic strategies for disorders characterized by social dysfunction. A growing body of literature suggests that the neuropeptide oxytocin (OXT) plays a critical role in modulating social behavior and may also be a necessary modulator of social reward. The present exploratory study aimed to elucidate the role of OXT in driving the rewarding effect of social interaction in Wistar rats using a social conditioned place preference (CPP) paradigm. Briefly, we employed a 10-day social conditioning paradigm, where subjects (n = 81) were conditioned to associate one of two distinct contexts with social interaction with a paired conspecific. In Experiment 1, we demonstrated that both male and female rats spent an increased amount of time in the socially-paired chamber on test day compared to baseline relative to animals that did not receive conditioning with a conspecific. In Experiment 2 to evaluate the role of OXT in driving this social preference behavior, OXT receptors (OXTR) were selectively knocked down through infusion of AAV-OXTR-shRNA in three neuroanatomical structures involved in reward processing: (1) the ventral tegmental area (VTA), (2) the nucleus accumbens (NAc), and the lateral septum (LS). Previous studies have demonstrated that these three structures are implicated in social behaviors. Subjects received OXTR shRNA infusions either into the VTA, NAc, or LS and then underwent the 10-day CPP paradigm. We then evaluated the amount of time spent in the socially-conditioned chamber relative to control animals. Animals demonstrated diminished social conditioned place preference following OXTR knockdown in the VTA, NAc, or LS, as measured by a decrease in time spent in the socially-paired chamber at test. These findings demonstrate OXTRs within the VTA, NAc, or LS are necessary and sufficient to mediate social preference behavior. This research further expands our understanding of the neural mechanisms underlying social reward.

Disclosures: J. Stall: None. **K. Leong:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.23/KK18

Topic: I.04. Executive Functions

Support: NIH Grant 5R01NS136371-02

Title: Anatomical and functional characterization of Oxytocin Receptor Positive Neurons in the dorsal Endopiriform Nucleus Projecting to the Infralimbic Cortex

Authors: *X. HAN;
Penn State Univ. Col. of Med., Hershey, PA

Abstract: Anatomical and functional characterization of Oxytocin Receptor Positive Neurons in the dorsal Endopiriform Nucleus Projecting to the Infralimbic Cortex
Authors Xiao Han[1], Yongsoo Kim[1]Dept. of Neuroscience and Experimental Therapeutics. Penn State College of Medicine, Hershey, PA, 17036
Oxytocin is an important neuropeptide and hormone that plays crucial roles in cognitive social behaviors. Previous studies in mice showed that oxytocin receptor positive (Oxtr+) neurons are highly enriched in the dorsal endopiriform nucleus (EPd).The input-output mapping of EPd Oxtr+ neurons unveils extensive bidirectional connections with limbic areas including the inflalimbic cortex (ILA). Moreover, EPd Oxtr+ neurons showed reduced activities when novel objects or strangers were presented, indicating that it could contribute to internal state regulation and behavioral adaptations to novel environmental cues (Manjila et al. 2025). However, it remains unknown which projection pathway this phenomenon attributes to, and how EPd Oxtr+ neuron activities influence their downstream targets. Here, we investigate the EPd-ILA connectivity, specifically understanding the types of neurons that EPd Oxtr+ innervated within the ILA and the neural dynamics of this pathway. Our retrograde rabies monosynaptic tracing showed that EPd Oxtr+ neurons are innervating both glutamatergic and GABAergic neurons in the ILA with a higher proportion to glutamatergic neurons. Next, we conducted fiber photometry recordings of projection fiber in the ILA from the EPd Oxtr+ neurons to understand the neural dynamics of this pathway. Results showed that activities of EPd Oxtr+ neurons to the ILA decreased its activities upon a novel object but surprisingly increased upon a novel stranger with opposite sex. These findings suggest that EPd Oxtr neurons may play a role in regulating social cognitive functions via their connection to the ILA.

Disclosures: X. Han: None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.24/KK19

Topic: H.03. Motivation

Support: MTSU URECA Grant

Title: Intra-Nucleus Accumbens Administration of Oxytocin Reduces Social Motivation in C57BL/6J Mice

Authors: T. MCALMOND[1], K. EVANS[4], J. KITTRELL[2], C. WELLS[2], A. MARRISON[3], *T. D. ROGERS[2];
[1]Middle Tennessee State Univ., Knoxville, TN; [2]Middle Tennessee State Univ., Murfreesboro, TN; [3]Middle Tennessee State Univ., Thompson's station, TN; [4]Middle Tennessee State university, Smyrna, TN

Abstract: Oxytocin (OT), a well-known neuromodulator associated with parental and social behavior, is proposed as a treatment for reduced social interaction and altered social communication in autism spectrum disorders (ASD). However, systemic OT administration has resulted in variable social behavior changes in recent clinical trials. Our previous research has demonstrated that systemic OT in C57BL/6J mice reduces social motivation as measured by novel social motivation tasks, the weighted door and ladder task. In the weighted door task, mice are required to push open a door with increasing weight to access a social partner (sex- and age-matched conspecific) across five successive trials. In the ladder task, mice are required to reach a social partner by climbing a ladder that becomes increasingly steep over five successive trials. We have also previously investigated the role of OT in the nucleus accumbens (NAc) during the social conditioned place preference (sCPP) test in C57BL/6J mice. Intra-NAc infusions of OT resulted in reduced social reward such that mice receiving OT did not display a preference for the social condition whereas mice receiving intra-NAc saline did prefer the social condition. Together these results suggest that OT receptor activation in the NAc may, in part, mediate OT's role in reducing social motivation. Building on our previous findings indicating OT in the NAc OT reduces social reward, the current study aims to measure changes in social motivation via the weighted door and ladder task following intra-NAc OT infusion in C57BL/6J mice. Bilateral cannulas were placed in the left and right NAc in male and female adult C57BL/6J mice. After recovery, mice underwent behavioral measures including measurement of social motivation, anxiety-like behaviors, and general sociability. Mice receiving intra-NAc OT displayed increased latency to access a social partner in the ladder and weighted door tasks and reduced time spent pushing on the weighted door in the weighted door task. These results are consistent with our previous findings suggesting that OT decreases social motivation and that intra-NAc OT receptor activity may play an essential role in mediating social motivation. Increasing our understanding of the role of OT in specific components of social behavior, such as social motivation, will further inform the use of OT in clinical settings and the development of novel pharmacological agents for ASD.

Disclosures: T. McAlmond: None. **K. Evans:** None. **J. Kittrell:** None. **C. Wells:** None. **A. Marrison:** None. **T.D. Rogers:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.25/KK20

Topic: I.06. Social Cognition

Support: NSERC RGPIN-2018-04699

Title: Rapid Effects of 17β-estradiol in the BNST on Short-Term Social Recognition Memory in Adult Female Mice

Authors: *H. AZIZI ZAWAR[1], E. ZAHEER[2], C. LAROCHELLE-COMPTON[3], E. CHOLERIS[4];
[1]Univ. of Guelph, Guelph, ON, Canada; [2]Univ. of Guelph, Mississauga, ON, Canada; [3]Univ. of Guelph, Calgary, AB, Canada; [4]Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Social recognition, the ability to distinguish between familiar and unfamiliar conspecifics, is a crucial part of social cognition that enables adaptive social interactions across species. Gonadal hormones, like estradiol and androgens, are known to modulate social recognition both via delayed genomic and rapid mechanisms. Previous work from our laboratory demonstrated that hormone delivery within the bed nucleus of the stria terminalis (BNST), a sexually dimorphic region that integrates social, emotional, and hormonal information, plays a critical role in regulating social recognition in males (Aspesi et al, 2026, PNAS). Whether these mechanisms generalize to females is unknown. The current study examines how 17β-estradiol, the most abundant and biologically active estrogen, influences social recognition through BNST signalling in 8-week-old ovariectomized female CD1 mice. Bilateral intracranial cannulae targeting the BNST are used to deliver 17β-estradiol directly into the region, thereby isolating rapid local hormone effects while minimizing systemic influences. Mice (N=12/group) will receive either vehicle or estradiol at one of 0.25 nM, 0.50 nM, or 100 nM doses fifteen minutes before testing for social recognition (Phan, 2008). Based on evidence that estradiol often produces non-linear, receptor-dependent effects, we hypothesize that social recognition will exhibit a dose-dependent response to BNST estradiol administration, with intermediate doses producing greater behavioural enhancement than low or high doses (Aspesi, 2023; Sheppard, 2018). This work addresses a significant gap in the literature by extending BNST hormone-signalling studies from males to females and provides insight into the neuroendocrine mechanisms underlying sex differences in social cognition. Findings from this research may inform future investigations examining estrogen receptor-specific signalling pathways and their contribution to socially relevant behaviours.

Disclosures: H. Azizi Zawar: None. **E. Zaheer:** None. **C. LaRochelle-Compton:** None. **E. Choleris:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.26/Web Only

Topic: I.06. Social Cognition

Support: NSERC - RGPIN-2018-04699

Title: Estrone's Rapid Effects in the Dorsal Hippocampus on Social Recognition in Female Mice.

Authors: *K. ANDREWS[1], K. ATMAJA[2], L. A. GALEA[3], E. CHOLERIS[1];
[1]Psychology, [2]Univ. of Guelph, Guelph, ON, Canada; [3]Djavad Mowafaghian Ctr. from Brain Health, Psychology, Univ. of British Columbia Grad. Program In Neurosci., Toronto, ON, Canada

Abstract: Estrogens are potent neuromodulators, known to influence a variety of cognitive functions, including social recognition, or the ability to learn about others. Social recognition is a fundamental skill in many species, influencing how we interact with others in real time. One site of estrogen action includes the hippocampus, where estrogens affect various types of memory, including social recognition. Though the delayed genomic effects of estrogens on cognition have received more attention, the rapid effects are less understood. Historically, most estrogen research has focused on the effects of 17β-estradiol, though several other estrogens, including estrone, naturally occur in humans and rodents alike. Though estrone is a "weak" estrogen with lower receptor binding affinity than 17β-estradiol, current research has demonstrated its profound and often differing effects from 17β-estradiol. Thus, investigating the impacts of different estrogens in the brain is necessary for understanding estrogens' influence on cognition. The present study investigated the rapid effects of bilateral infusions of estrone at concentrations of 50, 100, 150, and 200 nM in the dorsal hippocampus of young adult ovariectomized female CD-1 mice, on social recognition. By identifying estrone's rapid influence on social recognition, we can build a better understanding of the specific and often variable effects of different estrogens on the brain and their implications for social behaviour.

Disclosures: K. Andrews: None. **K. Atmaja:** None. **L.A. Galea:** None. **E. Choleris:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.27/KK21

Topic: H.03. Motivation

Title: The Role of Glucagon-like Peptide-1 Receptors in Mediating Social Motivation in C57BL/6J Mice

Authors: *K. EVANS[1], C. WELLS[4], A. MCGARRY-NOWAK[2], C. KIMBRELL[4], R. IKBARIAH[3], T. D. ROGERS[5];
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Abstract: Glucagon-like-peptide receptor (GLP-1R) agonists mimic endogenous secretion of GLP-1 hormones that play a crucial role in metabolic function including the regulations of glucose, slowing gastric emptying, and promoting satiety which in turn can promote weight loss. Although these functions may seem restricted to the gut, GLP-1Rs are expressed in the central nervous system and are associated with a variety of motivated behaviors and reward processing. In recent studies, GLP-1R agonists are associated with reduced consumption of substances of abuse and reduced drug seeking behaviors. Recent research also suggests that GLP-1R activation in the NTS reduces sociability. Given that GLP-1Rs may contribute to reward-motivated behavior and sociability, the current study aims to determine whether systemic injections of a GLP-1R agonist and a GLP-1R antagonist alter sociability or social motivation. We injected adult female and male C57 mice intraperitoneally with the GLP-1R agonist exendin-4 (Ex4) and the GLP-1R antagonist exendin-9 (Ex9) prior to social behavior measurement. Neither Ex4 nor Ex9 altered anxiety-like behavior as measured by the elevated plus maze. Likewise, neither Ex4 nor Ex9 altered sociability during a free dyadic social interaction (FDSI) test. However, both Ex4 and Ex9 altered social motivation as measured by the novel weighted door and ladder task which requires experimental mice to exert increasing effort, either pushing open an increasingly heavy weighted door or climbing an increasingly steep ladder, to access a social partner (same-sex, same-age conspecific). Ex4 and Ex9 administration increased the overall time spent exploring a weighted door but increased the latency to open the door. Additionally, alterations of social motivation displayed distinct patterns across trials demonstrating unique actions of the GLP-1R agonist and antagonist during low versus high effort trials. This study demonstrates that while GLP-1R agonism reduces motivation for food and drug-related rewards, social rewards may be uniquely impacted by GLP-1Rs. Further understanding of the role of GLP-1Rs in social reward is needed to better predict the behavioral impact of GLP-1Rs agonists in clinical settings.

Disclosures: K. Evans: None. **C. Wells:** None. **A. McGarry-Nowak:** None. **C. Kimbrell:** None. **R. Ikbariah:** None. **T.D. Rogers:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.28/KK22

Topic: H.03. Motivation

Support: NIH R01NS099288
NIH R01NS118424
Duke SoM International Chancellor's Scholarship

Title: Neural circuits for motivating skilled movements

Authors: *S. LI[1], R. D. MOONEY[2];
[1]Neurobio., [2]Duke Univ., Durham, NC

Abstract: The brain of a male zebra finch provides a powerful system to study neural mechanisms that motivate spontaneous versus stimulus-driven skilled movements. A male zebra finch spontaneously sings thousands of times a day to learn and maintain its complex song (known as undirected singing) and also sings reflexively when it sees a female (directed singing). Although both behaviors depend on a song-specialized cortico-basal ganglia network, little is known about how context-dependent motivational signals differentially recruit this network to drive undirected or directed singing. My initial experiment identified the medial preoptic area of the hypothalamus (POA) as a key driver for both types of singing. I hypothesize that distinct POA populations promote these behaviors through separate midbrain pathways, preferentially engaging VTA-projecting circuits during undirected singing and A11-projecting circuits during directed singing. Combining retrograde tracing and in situ hybridization, I found that distinct populations of POA neurons send predominantly inhibitory projections to VTA and A11. Ongoing single-nucleus RNA sequencing has further revealed distinct POA cell clusters expressing genes associated with courtship behavior, vocal-motor control, and auditory processing, which I aim to relate to their projection-specific identity. Moreover, fiber photometry imaging showed that these POA axons in VTA are preferentially active during undirected singing, whereas POA axons in A11 are more active during directed singing. I am now testing how these POA pathways bias context-specific singing through projection-specific optogenetic manipulations. Given that POA-midbrain circuitry is highly conserved across vertebrates, these findings may reveal general principles by which hypothalamic circuits motivate spontaneous versus stimulus-driven skilled movements.

Disclosures: S. Li: None. **R.D. Mooney:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.29/KK23

Topic: H.03. Motivation

Support: KBRI 23-BR-01-01, 24-BR-01-01, 25-BR-01-01

Title: Stress-induced persistent reduction of intrinsic motivation for undirected singing in zebra finches: a potential songbird model of depression

Authors: *O.-Y. JEONG[1], Y. KIM[2], S. KOJIMA[3];
[1]DGIST (Daegu Gyeongbuk Inst. of Sci. and Technology), Daegu, Korea, Republic of; [3]Sensory and Motor Systems Res. Group, [2]Korea Brain Res. Inst., Daegu, Korea, Republic of

Abstract: Male zebra finches spontaneously produce non-courtship (“undirected”) songs hundreds of times per day even in the absence of immediate external rewards, making them as an excellent model system for studying intrinsic motivation. Intrinsic motivation drives various spontaneous behaviors in animals, including humans, and its reduction is one of the primary

symptoms of mood disorders such as depression. However, intrinsic motivation has received little attention in existing rodent models of depression, mainly due to the difficulty of quantifying intrinsic motivation in rodents. In contrast, in zebra finches, the intrinsic motivation for undirected singing can be easily and continuously monitored by recording their songs. Taking advantage of this, we attempted to establish a new animal model of depression that specifically focuses on intrinsic motivation using zebra finches. Drawing on previous studies using rodent models of depression, we subjected birds to chronic physical stress (restraint using a conical tube for 4 hours per day over a total of 10 days) and examined the effects on the production of undirected songs. We found that in many birds, undirected singing rate decreased significantly during and following the stress exposure period and did not fully recover over the subsequent two weeks. In addition, we measured plasma corticosterone (CORT) levels before, during, and after the stress exposure, and found that CORT levels rose during the stress period but quickly returned to baseline levels after the stress exposure. These results suggest that elevated plasma CORT levels during the stress exposure may lead to a persistent reduction in intrinsic motivation, as shown for other depressive symptoms in rodent models. We are currently investigating the effect of physical stress on behaviors other than undirected singing to further assess the validity of this songbird model of depression. Together, our results demonstrate that chronic physical stress induces a persistent reduction of intrinsic motivation in zebra finches, supporting the potential utility of songbirds as an animal model for investigating stress-induced depression-like behavior and its recovery mechanisms.

Disclosures: O. Jeong: None. **Y. Kim:** None. **S. Kojima:** None.

Poster

PSTR075: Behavioral and Circuit Mechanisms of Social Behavior I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR075.30/KK24

Topic: H.03. Motivation

Title: Emergence of social deficits and blunted basolateral amygdala activity in a rodent model of excessive audiovisual stimulation

Authors: *A. PORRAS[1], M. RINCÓN-CORTÉS[2];
[2]Neurosci., [1]Univ. of Texas at Dallas, Richardson, TX

Abstract: The last two decades have been marked by a prevalent rise in technology and digital media, which has been linked to increased risk for social dysfunction as well as psychiatric disorders characterized by social dysfunction such as mood and autism spectrum disorders (Sundarimaa et al., 2025; Sarfraz et al., 2023; Kim et al.,2023). We used a rodent model of daily sensory overstimulation (SOS) involving flashing lights synchronized with children's programming audio from postnatal day (PND) 10-40 to assess how early-life SOS affects social behavior and relevant brain function in adolescent rodents given that our previous study found a social deficit in SOS females during late adolescence (PND56) (Porras et al., 2024). To explore

the onset of SOS-induced social deficits and its potential neurobiological underpinnings, we incorporated longitudinal social behavior assays in rats of both sexes and examined associated neural correlates using c-Fos immunohistochemistry. We hypothesize that SOS-induced social deficits would emerge prior to adolescent and be linked to altered neural activation patterns across multiple brain regions implicated in social behavior (e.g., nucleus accumbens, basolateral amygdala, ventral tegmental area). Our findings revealed significant reductions in juvenile social play in females at PND30 (n=6-9 per group; p= 0.001) and reductions in both sexes at PND32 (females n=8 p/g p= 0.03; males: n=8-9 p/g, p= 0.04) and PND34 (females: n=7-9 p/g; p= 0.04; males: n=8 p/g, p= 0.02). At PND35, social motivation was significantly reduced in both sexes (females: n=8-9 p/g, p= 0.04; males: CON: n=8-9 p/g, p= 0.04), with effects persisting into adolescence (PND45) only in SOS females (n=8-9 p/g, p= 0.04). In addition, we report a significant decrease in the number of c-Fos + neurons (PND 45; females: n=7-9 p/g, p= 0.009) in the basolateral amygdala of SOS females only. Together, these findings support age and sex-specific social motivation vulnerabilities following early-life SOS. Ongoing c-Fos studies are examining neural changes associated with behavioral effects seen in both sexes at the PND 35 timepoint. Importantly, these data highlight the need to investigate early-life digital media and its associated effects on social behavior and reward system development.

Disclosures: A. Porras: None. **M. Rincón-Cortés:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.01/KK25

Topic: I.08. Learning and Memory

Support: NIA R00AG056596
NIA R21AG068444
Whitehall #2020-05-06
AFAR #A21105
NIH R01AG074041

Title: Differential mechanisms of diurnal memory across the lifespan in female mice

Authors: *G. C. PIFER[1], L. BELLFY[2], J. L. KWAPIS[3];
[1]Biol., Pennsylvania State Univ., University Park, PA; [2]Broad Inst. of MIT and Harvard, Cambridge, MA; [3]Dept. of Biology, Ctr. for Mol. Investigation of Neurolog. Disord, Penn State Univ., University Park, PA

Abstract: Long-term memory persists over an extended period of time, operationally defined as 24+ hours following memory acquisition. Our lab has previously shown that long-term memory performance on the hippocampus-dependent Objection Location Memory (OLM) task is different across the diurnal cycle, depending on age and sex. Additionally, we have shown that

the circadian gene *Per1* oscillates in tandem with memory performance in young males and aged females, with the peak of expression occurring during the day when memory is best. Conversely, young females show good memory across the entirety of the diurnal cycle, and no significant induction of *Per1*. While this suggests that *Per1* may play a non-canonical role within the dorsal hippocampus (DH) in young male and aged female mice, it appears that young female mice may be engaging a divergent mechanism that enables their strong memory performance across the 24-hour day. One possible mechanism could be E_2, a potent form of estrogen that is expressed highly in young female mice and drops precipitously with age. Supporting evidence from our lab shows that OLM performance is significantly worse during diestrus, the estrous phase with the lowest E_2 concentration, and that young female mice who have undergone ovariectomies display oscillatory memory patterns matching those of young males. Additionally, *Per1* compensation occurs within the DH of ovariectomized female mice. Together, our work suggests that E_2 can overcome *Per1*'s ability to diurnally regulate memory, and disruption of estradiol enables *Per1* to re-exert this diurnal control. Further research is necessary to elucidate exactly how *Per1* and E_2 are interacting at a molecular level to facilitate these behavioral patterns.

Disclosures: G.C. Pifer: None. **L. Bellfy:** None. **J.L. Kwapis:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.02/KK26

Topic: I.08. Learning and Memory

Support: Office of Naval Research (ONR) grant N00014-19-1-2373
Neuro-omics Project supported by Wu Tsai Neurosciences Institute
NIH grant R35GM130366
Whitman Early Career Award
Stanford Genomics Training Program 5T32HG000044–22
Stanford Wu Tsai Neurosciences Institute Interdisciplinary Scholar Fellowship

Title: Activity-dependent gene regulation in a learning and memory circuit of the octopus brain

Authors: *E. HWAUN[1,2], M. MCCOY[4], J. SZABADICS[5], G. G. SZABO[3], W. F. GILLY[6], I. SOLTESZ[2];
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Abstract: The deep evolutionary divergence between cephalopods and vertebrates offers a rareopportunity to examine how complex neural circuits are built from conserved and lineage-specific molecular components. In octopus, associative learning relies on the superior frontal-vertical lobe system, an anatomically compact yet neuron-dense circuit essential for memory-

guided behavior. Leveraging chromosome-scale genomes and deep-learning approaches, wecombined single-nucleus profiling of gene expression and chromatin accessibility with single-cell electrophysiology to identify distinct neuronal classes and show that neuronal activityengages conserved transcriptional programs alongside expanded zinc-finger regulators. Activity-dependent gene induction is accompanied by changes in sodium currents, pointing to jointregulation of transcription and neuronal function. These findings reveal lineage-specificregulatory innovations layered onto a shared logic of activity-dependent transcriptional plasticitythat likely contributed to the evolution of cephalopod cognition.

Disclosures: E. Hwaun: None. **M. McCoy:** None. **J. Szabadics:** None. **G.G. Szabo:** None. **W.F. Gilly:** None. **I. Soltesz:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.03/KK27

Topic: I.08. Learning and Memory

Support: ANID-MILENIO NCN2023_32 (FJB)
FONDECYT Regular Grant 1250955 (FJB)
FONDECYT Regular Grant 1230454 (LVN)
Pew Trust repatriation fund (FJB)

Title: A putative activity-dependent DNA enhancer sequence controls the expression of an Immediate Early Gene associated to synaptic plasticity

Authors: *C. AHUMADA[1], C. LOPEZ-ESCOBILLANA[2], M. PEDRAZA[3], B. VAN ZUNDERT[2], L. VARELA-NALLAR[2], F. J. BUSTOS[3];
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Abstract: Neuronal activity induces transcriptional programs that support synaptic plasticity. Immediate early genes (IEG) play a critical role in activity-dependent transcription and neuronal plasticity. However, the regulatory elements controlling its rapid activity-dependent expression remain poorly understood. Epigenomic analyses of hippocampal engram neurons following contextual fear conditioning identified a putative regulatory sequence of upstream IEGs promoters enriched in histone marks H3K4me1 and H3K27ac. To determine whether this sequence regulates the expression of a specific IEG, we employed CRISPR-based genetic and epigenetic editing approaches. sgRNAs were designed and validated using T7 endonuclease I assays. The sequence was subsequently manipulated through CRISPR/Cas9-mediated deletion and locus-specific epigenetic editing with dCas9-p300 and dCas9-HDAC8 in primary

hippocampal neurons and whole mouse brain. Successful deletion of the sequence was confirmed in vitro and in vivo by sequencing, genomic PCR, and gDNA qPCR analyses (4 = cultures; n = 4 mice). In primary hippocampal neurons, sequence deletion tended to reduce activity-dependent IEG expression following KCl-induced depolarization (n = 4 independent cultures, Wilcoxon test, p = 0.1465). Targeted epigenetic activation by dCas9-p300-mediated acetylation increased IEG expression after neuronal stimulation (n= 3 independent cultures, one-way ANOVA test, p= 0.0088). Conversely, targeted deacetylation using dCas9-HDAC8 tended to reduce IEG expression, supporting a role for acetylation in IEG transcriptional regulation. Consistent with these findings, in vivo activation of the same region increased basal IEG expression following viral delivery (n= 4 mice, Student's t-test, p=0.0002). Our findings suggest that the predicted sequence functions as a regulatory element that modulates activity-dependent IEG expression.

Disclosures: C. Ahumada: None. **C. Lopez-Escobillana:** None. **M. Pedraza:** None. **B. Van Zundert:** None. **L. Varela-Nallar:** None. **F.J. Bustos:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.04/KK28

Topic: I.08. Learning and Memory

Title: Inflammatory pain during pregnancy induces cognitive impairment in male offspring via hippocampal XLR3B dysregulation

Authors: *Z. LI[1], X. LI[1], F. HARERAM[1], Q. ZHANG[1], K. MATSUO[2], N. SHIODA[3], Y. XU[1], J. CAO[1], Y. TAO[1], H. HU[1];
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Abstract: It is well established that prenatal adverse stimuli can negatively affect cognitive development and increase the risk of disease in adulthood. Animals exposed to prenatal stress often exhibit various cognitive deficits accompanied by alterations in brain plasticity. However, the effects of pathological pain during pregnancy on offspring neurodevelopment remain largely unknown. Here, we aimed to investigate whether maternal inflammatory pain represents a risk factor affecting cognitive development in offspring. Pregnant dams received an intraplantar injection of complete Freund’s adjuvant (CFA) at gestational day 9 (GD9) to induce inflammatory pain. Male offspring from CFA-exposed dams exhibited significant cognitive deficits in multiple hippocampus-dependent behavioral tasks, including novel object recognition, Y-maze spontaneous alternation, and the Morris water maze. Interestingly, these behavioral changes were not observed in the female offspring. To assess locomotor activity and anxiety-like behavior in offspring from dams exposed to either Saline or CFA, we conducted open-field and elevated-plus maze tests in male and female offspring. Surprisingly, we did not observe any

significant behavioral differences between the offspring from CFA-exposed dams and those from Saline-exposed dams, suggesting that the cognitive impairment observed was not due to alterations in locomotor activity or anxiety-like behavior. Western blot analyses showed that male offspring displayed increased hippocampal expression of X-linked lymphocyte-regulated protein 3B (XLR3B), accompanied by reduced BDNF levels. In addition, impaired dendritic spine morphology and attenuated hippocampal long-term potentiation (LTP) were observed, suggesting disrupted hippocampal synaptic plasticity. To further assess the functional role of *Xlr3b*, we used viral-mediated hippocampal *Xlr3b* overexpression, which increased XLR3B protein levels, reduced BDNF expression, and induced cognitive deficits. These findings suggest that maternal inflammatory pain may impair hippocampal synaptic plasticity, potentially leading to cognitive deficits by upregulating hippocampal XLR3B/BDNF in male offspring. Our study provides a potential mechanism for the sex differences in neurodevelopmental abnormalities associated with maternal inflammatory pain.

Disclosures: Z. Li: None. **X. Li:** None. **F. Hareram:** None. **Q. Zhang:** None. **K. Matsuo:** None. **N. Shioda:** None. **Y. Xu:** None. **J. Cao:** None. **Y. Tao:** None. **H. Hu:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.05/KK29

Topic: I.08. Learning and Memory

Support: NIMH Diversity Supplement R01MH1210133 - S1
HHMI Gilliam Fellowship
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Canadian Institute for Advanced Research
USC Neuroscience Graduate Program
The Saban Research Institute
Developmental Neuroscience and Neurogenetics Program
TSRI Animal Care Facility

Title: Learning and memory in Prader-Willi Syndrome through the lens of snord116 in catecholaminergic cells

Authors: *L. S. VASQUEZ[1], S. STACK[2], B. G. DIAS[3];
[1]Neurosci. Grad. Program, USC, Los Angeles, CA; [2]Neurosci. Grad. Program, USC, LOS ANGELES, CA; [3]Pediatrics, Keck Sch. of Med., Los Angeles, CA

Abstract: Prader-Willi Syndrome (PWS) results from deletion of paternal alleles on chromosome 15 and is characterized, in part, by altered learning and memory. Of the paternal alleles deleted, loss of the non-coding RNA *snord116*, in mice and humans, disrupts learning and memory. However, cell-type-specific contributions of *snord116* to learning and memory remain

unexplored. Given their role in learning and memory and their distinct regional organization throughout the brain, catecholaminergic cells are an ideal population to focus on to fill this gap. Using a CRE-LoxP approach, we first knocked-out paternal *snord116* in all catecholaminergic cells (Cat-KO) of the mouse brain and measured learning and memory, using auditory fear conditioning (AFC), extinction training, and extinction recall tests. Next, using intra-cranial infusions of CRE-recombinase directly into the VTA, we determined how knocking out paternal *snord116* in the VTA (VTA-KO) influenced learning and memory. All animals acquired fear during AFC and extinguished their fear during extinction training. Both, Cat-KO and VTA-KO males exhibited enhanced retrieval of extinction memory during the extinction recall test. In contrast, Cat-KO females showed impaired retrieval of extinction memory compared to Cat-INTACT females. VTA-KO females did not show any alterations in learning and memory. Our data suggest that the paternal allele of *snord116* contributes to learning and memory in a sex-, cell- and region-specific manner. These findings lay the foundation for identifying sex-, cell- and region-specific molecular mechanisms underlying learning and memory challenges associated with paternal *snord116* loss in general, and more specifically, in PWS.

Disclosures: L.S. Vasquez: None. **S. Stack:** None. **B.G. Dias:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.06/KK30

Topic: I.08. Learning and Memory

Support: NSF Grant IOS-1942202
UNO Research Development Program Grant
UNO GRACA Grant

Title: Neurotranscriptome contribution to differences in learning between personality type in zebrafish (Danio rerio)

Authors: *J. CORCORAN[1], L. STORKS[2], R. Y. WONG[3];
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Abstract: Learning and memory are important processes that allow animals to acquire new knowledge about their environment in order to survive. Animals differ in behavior on an individual level, including cognitive ability and stress coping style. Studies of associative learning across multiple taxa find that proactive animals learn faster and that reactive fish remember associations for longer amounts of time. It has been shown that coping styles differ in gene expression, mainly in neurometabolism and oxidative stress at baseline. These baseline differences could explain cognitive variation however, exploring the neurotranscriptome while learning and remembering provides a more direct link to learning and memory ability and can

reveal additional mechanisms for the variation in learning and memory across coping style. Investigating expression in specific brain regions related to learning also provides a more direct link for transcriptomic differences to behavior. We investigated differences in RNA expression in proactive and reactive fish undergoing an associative learning task with a food reward. We specifically looked at the transcriptomes in Dm (amygdala homolog) and Dl (hippocampal homolog) as these areas are important for learning and have shown differences between coping style previously. We tested fish during conditioning and during recall to represent fish undergoing the learning process and fish that are remembering the association. We found that all treatment fish learned the association. Interestingly, we found that there were no differences in learning speed between proactive and reactive fish, despite previous data. While this suggests that there were no differences in learning, the baseline expression data suggests that there may be different molecular mechanisms between stress coping style to achieve similar learning rates. We found differences in gene expression in the Dm and Dl between proactive and reactive fish in learning and memory groups that suggest potential mechanisms for differences in learning. This study provides possible mechanisms for the link between stress coping style and learning. These mechanisms may lead to potential interventions for difficulties with cognition related to stress.

Disclosures: J. Corcoran: None. **L. Storks:** None. **R.Y. Wong:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.07/KK31

Topic: I.08. Learning and Memory

Support: Pew Foundation

Title: Rem2 regulates the formation of learning-related CA1 spatial representations

Authors: *Y. ZHANG, S. PARADIS, C. GRIENBERGER;
Brandeis Univ., Waltham, MA

Abstract: The formation of experience-dependent representations in hippocampal area CA1 is a fundamental neural computation supporting spatial learning. During exploration of a novel environment, CA1 pyramidal neurons acquire place fields through behavioral timescale synaptic plasticity (BTSP). While the circuit mechanisms underlying BTSP are increasingly well understood, the molecular pathways that regulate BTSP during learning remain largely unknown. Rem2 is an activity-regulated small GTPase implicated in experience-dependent neuronal plasticity. Acute Rem2 deletion in adult mice alters dendritic morphology and ocular dominance plasticity in the visual cortex and enhances long-term potentiation in acute hippocampal slices by modulating CaMKII signaling. These findings identify Rem2 as a candidate regulator of learning-related plasticity. However, whether Rem2 contributes to BTSP in CA1 pyramidal neurons *in vivo* and whether it is required for the formation of hippocampal spatial

representations during learning remain unknown. To address this question, we used in vivo two-photon calcium imaging to monitor CA1 population activity while mice learned the location of a fixed sucrose reward in a novel, cue-rich environment. Rem2 was deleted in CA1 pyramidal neurons in Rem2-floxed mice through AAV-mediated expression of Cre recombinase tagged with the fluorescent protein tdTomato (tdT). Wildtype mice expressing the same Cre-tdT virus that were treated the same otherwise served as controls. Consistent with a role for Rem2 in the formation of experience-dependent representations, Rem2 deletion significantly reduced the fraction of neurons classified as place cells, abolished the characteristic overrepresentation of place fields at rewarded locations, and reduced trial-to-trial reliability in those place cells that did form. Preliminary analyses suggest that BTSP is not abolished by Rem2 loss but is instead dysregulated, resulting in abnormal place field formation. Together, these findings identify Rem2 as a candidate molecular regulator of BTSP and suggest that it contributes to the formation of learning-related hippocampal representations.

Disclosures: Y. Zhang: None. **S. Paradis:** None. **C. Grienberger:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.08/KK32

Topic: I.08. Learning and Memory

Support: FAPESP 2021/06287-6
FAPESP 2024/00317-9

Title: Conditional Knockout of Protein disulfide isomerase a3 in Neurons Leads to Memory Deficits

Authors: *N. PEREIRA[1,2], P. A. OJEDA[3,4,5,6], G. QUIROZ[7], D. CONTRERAS PACHECO[8], F. MELLEU[9], J. N. DOS PRAZERES[2], F. GODOY[10], C. A. ROZAS[10], B. E. MORALES[10], N. S. CANTERAS[9], C. HETZ[4,5,6,11], D. BILCHES MEDINAS[2,4,5,6];
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Abstract: Protein homeostasis (proteostasis) of the endoplasmic reticulum (ER) is crucial for organism development and functioning. Unbalance of ER proteostasis can cause degenerative

and congenital disorders frequently involving neurological deficits. Protein disulfide isomerases (PDIs) are oxidoreductases catalyzing redox protein folding in the ER. PDIA3 is a major paralog widely implicated in neurological disorders, highlighting its causal association with intellectual disability. To define PDIA3 role in learning and memory, we used Cre-Lox system to ablate *Pdia3* in forebrain neurons (*Pdia3*^{cKO}), including CA1 hippocampal pyramidal neurons, followed by behavioral, histological, and biochemical analyses. Immunofluorescence showed PDIA3 presence in CA1 pyramidal neurons of wild-type (*Pdia3*^{WT}) mice and its absence in *Pdia3*^{cKO} mice. Quantitative RT-PCR corroborated successful gene ablation in the hippocampus. In the open field test, *Pdia3*^{cKO} mice behaved similarly to *Pdia3*^{WT} littermates (*Pdia3*^{WT} n=25; *Pdia3*^{cKO}, n=28), revealing that *Pdia3* deletion neither compromises locomotion nor generates anxiety. In the novel object localization test, *Pdia3*^{WT} animals preferred the relocated object while *Pdia3*^{cKO} demonstrated no preference, indicating that acquisition of spatial memory is compromised upon *Pdia3* deletion (t-test $p<0.05$; *Pdia3*^{WT}, n=25; *Pdia3*^{cKO}, n=28). In the Barnes maze, *Pdia3*^{cKO} mice covered greater distances and took longer to find the hiding place than *Pdia3*^{WT} littermates one-week post-learning, indicating deficits in long-term memory (learning curves two-way ANOVA p=0.0223; spatial memory t-test p=0.0371; *Pdia3*^{WT}, n=25; *Pdia3*^{cKO}, n=28). Morphometric Sholl analysis of CA1 pyramidal neurons labeled with Golgi-Cox staining revealed increased complexity of basal dendritic tree (two-way ANOVA $p<0.05$; *Pdia3*^{WT}, n=7; *Pdia3*^{cKO}, n=8). Furthermore, electrophysiological studies demonstrated reduced long-term potentiation of the CA3-CA1 synapse in *Pdia3*^{cKO} animals (statistical analysis performed using ANOVA with Sidak's multiple comparisons test $p<0.05$ *Pdia3*^{WT}, n=4,8; *Pdia3*^{cKO}, n=5,7). In summary, conditional *Pdia3* deletion in CA1 pyramidal neurons indicates that PDIA3 deficiency compromises neuronal morphogenesis and synaptic plasticity, leading to cognitive deficits.

Disclosures: N. Pereira: None. **P.A. Ojeda:** None. **G. Quiroz:** None. **D. Contreras Pacheco:** None. **F. Melleu:** None. **J.N. Dos prazeres:** None. **F. Godoy:** None. **C.A. Rozas:** None. **B.E. Morales:** None. **N.S. Canteras:** None. **C. Hetz:** None. **D. Bilches Medinas:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.09/KK33

Topic: I.08. Learning and Memory

Support: NRF Research Development Grants for Rated Researcher (CSRP230514105972/YRGR) and NMU Postgraduate Research Scholarship.

Title: THC addiction is linked to cognitive impairment in adolescent mice, associated with FosB and Let-7d expression changes

Authors: *A. MUSA;
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Abstract: Cannabis triggers heightened incentive salience within the mesocorticolimbic system and overlapping brain regions involved in memory and cognition. The legalization of cannabis over the past decade has made it more accessible and widely used. This places individuals with a genetic susceptibility at risk of developing cannabis use disorder (CUD). The mechanisms that drive neuroplastic changes in CUD are not well understood. This study explores health and safety concerns surrounding the impact of cannabis legalization on the adolescent brain and the potential maladaptive behavioral phenotypes associated with cannabis use. Twenty-four male C57BL/6 mice were randomly divided into four groups (n=6 per group) and received a Cremophor/saline solution (control), THC (5 mg/kg), CBD (20 mg/kg), or both within the conditioned place preference (CPP) apparatus to evaluate cue-induced drug-seeking behavior. Anxiety-like behavior was assessed using the open field test (OFT) and elevated plus maze (EPM), while cognitive performance was evaluated using the novel object recognition test. Thereafter, drug-induced transcriptional changes and miRNA profiling were assessed in the prefrontal cortex and hippocampus using RT-qPCR. 7days of THC exposure significantly increased the time spent in the least-preferred compartment compared to control ($p<0.05$), whereas CBD produced an opposite effect. THC also upregulated miRNA let-7d in both PFC and hippocampus ($p<0.05$), while co-exposure to CBD and THC significantly increased PFC ΔFosB expression ($p<0.05$). Phytocannabinoid exposure did not alter exploratory or anxiety-like behavior ($p>0.05$), but THC-treated mice showed impaired discrimination memory. In conclusion, we demonstrated that exposure to THC induces place preference, while CBD induces place aversion, and coadministration of CBD and THC produced an overall THC-like effect rather than a CBD-like effect. This was underpinned by transcriptional and epigenetic changes in the prefrontal cortex and hippocampus, involving FOSB and miR-let7d. These molecular changes may have neurocognitive implications. Thus, THC consumption can lead to addiction-like phenotypes. The study seeks to inform policies around cannabis legalization and encourage research into the safety profiles of phytocannabinoids.

Disclosures: A. Musa: None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.10/KK34

Topic: I.08. Learning and Memory

Support: Advancing Discovery to Market (ADM) award from the Division of Research, Texas A&M University
NIEHS P30ES029067
Seed Grant from the College of Arts and Sciences, Texas A&M University
USDA-ARS 58-3091-1-018

Title: Role of hippocampal AhR in consolidation of spatial memory and spatial precision

Authors: N. G. RODRIGUEZ[1], D. T. SLODOWITZ[2], C. LEVEN[1], J. HUTTON[1], S. PILON[1], *S. EITAN[3,1];
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Abstract: The aryl hydrocarbon receptor (AhR) is a nuclear transcription factor that acts as a regulator of physiological homeostasis through interactions with dietary, microbial, and endogenous tryptophan metabolites. Notably, recent research suggests that AhR signaling influences cognition. Therefore, in this study, we generated conditional AhR knockout mice in which AhR expression was nullified in the hippocampus (AhRΔHIPPO). AHR-floxed mice were stereotaxically administered into the hippocampus with AAVs (adeno-associated virus) expressing Cre-recombinase or AAV controls. Subsequently, mice were examined for general activity, anxiety, and cognition. AhRΔHIPPO mice exhibited a slight increase in locomotion as compared to controls. However, no differences were observed in anxiety as measured in the open field test (OFT) and dark/light tests. Additionally, mice underwent the Barnes maze, which consists of 3 phases: (1) Acquisition: 5 days of training (3 trials daily) to locate the escape box; (2) Probe: 1 trial with the escape box removed; and (3) Reversal: 3 trials with the target relocated 180° from the original location. During the acquisition phase, both AhRΔHIPPO and control mice demonstrated equivalent learning. During the probe phase, AhRΔHIPPO and control mice exhibited similar latency to locate the target. However, AhRΔHIPPO mice exhibited significant deficits in spatial precision. Specifically, although AhRΔHIPPO mice retained the correct quadrant on the probe, they committed significantly more errors, utilized an inferior search strategy, and were relatively imprecise compared to control mice. Nonetheless, during the reversal phase, AhRΔHIPPO mice located the new target location faster than control mice. However, this apparent increased cognitive flexibility of the AhRΔHIPPO mice is likely due to diminished precise spatial consolidation. During reversal, control mice exhibited robust perseveration to the original target location and progressively suppressed this perseveration across trials, whereas AhRΔHIPPO mice did not perseverate and did not improve on critical precision measures across sessions. This further supports improved memory consolidation of prior learning by the control mice as compared to AhRΔHIPPO mice, which introduces a conflict and a challenge less evident in the AhRΔHIPPO mice. In summary, this study highlights the importance of hippocampal AhR expression for consolidation of precise spatial location information.

Disclosures: N.G. Rodriguez: A. Employment/Salary (full or part-time):; Texas A&M University. **D.T. Slodowitz:** None. **C. Leven:** None. **J. Hutton:** None. **S. Pilon:** None. **S. Eitan:** A. Employment/Salary (full or part-time):; Texas A&M University.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.11/KK35

Topic: I.08. Learning and Memory

Support: NSERC

Title: Cyclic AMP/CaMKIIβ-dependent regulation of hippocampal CA1 neuronal activity underlying contextual fear memory retrieval

Authors: *J. RAI[1], J. IGLAR[2], H. LI[3], M. ZHEN[4], K.-I. OKAMOTO[5];
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Abstract: In the brain, long-term memories are not fixed permanently, they become labile upon retrieval, enabling updates such as erasure, enhancement, or integration of new information to facilitate adaptation to changing environments, which is a fundamental mechanism of cognitive function.
Here, we investigate the role of cAMP (adenosine 3′,5′-cyclic monophosphate: a ubiquitous secondary messenger) and CaMKIIβ (calcium/calmodulin dependent protein kinase type IIβ: an abundantly expressed postsynaptic enzyme which serves for synaptic potentiation) in hippocampal CA1 neurons underlying contextual fear memory retrieval using activity-dependent cAMP/CaMKIIβ manipulation and fiber-based calcium imaging in freely-behaving mice.
To identify and specifically manipulate cAMP/CaMKIIβ in the CA1 neurons which were active during contextual fear conditioning (CFC) for the induction of contextual fear memory, we virally expressed cAMP metabolic enzymes or CaMKIIβ mutants with a fluorescent marker NLS-RFP using a Dox OFF-inducible robust activity marking (RAM) system.
First, we examined the effect of cAMP manipulation in strongly activated neurons during CFC using a constitutive active form of phosphodiesterase-4B (PDE4cat) to suppress cAMP levels and a light-sensitive cAMP actuator bPAC (Photoactivatable Adenylyl Cyclase) to increase cAMP by light. During the 24h CFC test, cAMP suppression specifically in active CA1 neurons resulted in weak freezing behavior, indicating a deficit of contextual fear memory retrieval. Mice with activity-dependent co-expression of PDE4cat and bPAC in the active CA1 neurons also exhibit a similar suppression of memory retrieval, but this deficit was rescued by bPAC photoactivation (with constitutive PDE4cat activity) to light-dependently synthesize cAMP during retrieval.
To identify the cAMP effect on CA1 neuronal activity, we virally coexpressed GCaMP8m under CaMKII promoter with activity-dependent NLS-RFP/PDE4cat. By using NLS-RFP as a marker for active neurons during CFC, we compared the frequency and duration of calcium events between active and inactive CA1 neurons between control and cAMP suppression mice and observed that calcium activities were perturbed by cAMP suppression during retrieval.
Further, we tested the role of CaMKIIβ in contextual fear memory retrieval by expressing mutants which block activity-dependent dissociation from actin filaments (with suppression of endogenous CaMKIIβ) in active CA1 neurons during CFC and found that dissociation is required for memory retrieval. These results suggest a fundamental regulatory role of cAMP/CaMKIIβ in memory maintenance and retrieval.

Disclosures: J. Rai: None. **J. Iglar:** None. **H. Li:** None. **M. Zhen:** None. **K. Okamoto:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.12/KK36

Topic: I.08. Learning and Memory

Support: NIH Grant AG017628

Title: Sleep loss impairs protein synthesis required for memory

Authors: J. PATEL[1], J. M. MCCARTHY[2], S. P. FEENEY[3], *J. C. TUDOR[1];
[1]Biol., St. Joseph's Univ., Philadelphia, PA; [2]Univ. of Michigan, Ann Arbor, MI; [3]Univ. of Iowa, Iowa City, IA

Abstract: Sleep is a crucial biological process for all living organisms and is essential for both physical health and cognition. Sleep loss is known to produce deficits in protein synthesis in the hippocampus that leads to impaired hippocampus-dependent memory storage. This is due to characterized changes in mammalian target of rapamycin (mTOR) and eukaryotic initiation factor 4E-binding protein 2 (4EBP2) signaling. It has not yet been characterized whether this important regulator of cellular metabolism is also affected in other brain regions leading to impaired protein synthesis. In this study, we investigated the impact of a single 5-hour bout of sleep deprivation as well as a chronic 7-day sleep restriction on protein synthesis in multiple brain regions in both male and female mice. We found that sleep deprivation impairs protein synthesis uniquely in males and females in different brain regions. Females exposed to chronic sleep restriction are resilient to its effects, while males have impaired protein synthesis in the hippocampus and cerebellum. Similarly, a single bout of sleep deprivation has differing impacts in males and females. This underscores the need for continued research examining how males and females are differentially affected by sleep loss and its subsequent impact on cognition.

Disclosures: J. Patel: None. **J.M. McCarthy:** None. **S.P. Feeney:** None. **J.C. Tudor:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.13/KK37

Topic: I.08. Learning and Memory

Support: Estancias Posdoctorales por México (SECIHTI)
Departamento de Ciencias de la Salud

Title: Obesogenic diet disrupts hippocampal dopaminergic homeostasis and memory retention : Protective effects of environmental novelty

Authors: *S. HERNÁNDEZ-RAMÍREZ[1], E. CORDERO[2], K. R. GUZMAN-RAMOS[3]; [2]Ciencias de la Salud, [1]Univ. Autónoma Metropolitana, Lerma de Villada, Mexico; [3]Ciencias de la Salud, Univ. Autónoma Metropolitana, Lerma, Mexico

Abstract: Chronic exposure to obesogenic diets is linked to metabolic dysfunction, neuroinflammation, and cognitive decline. Environmental novelty promotes experience-dependent plasticity and may mitigate the adverse effects of hypercaloric diets on brain function. This study evaluated whether continuous exposure to housing changes, achieved through regular introduction and rearrangement of objects within the home cage, prevents cognitive deficits induced by chronic consumption of an hypercaloric diet from weaning and whether such effects are associated with alterations in hippocampal dopaminergic signaling and neuroinflammatory profiles To address this question, spatial memory performance, hippocampal dopaminergic markers (tyrosine hydroxylase [TH] and dopamine transporter [DAT]), and neuroinflammatory profiles were assessed in mice subjected to a high-fat, high fructose diet and environmental novelty interventions. Chronic exposure to a high-fat, high-sucrose diet from weaning altered metabolic function and impaired long-term spatial memory performance while preserving task acquisition, indicating alterations in memory retention and spatial memory precision rather than initial learning. These behavioral deficits were accompanied by reduced expression of TH and DAT in the dorsal hippocampus. Furthermore, neuroinflammatory markers revealed distinct inflammatory profiles associated with diet and environmental enrichment conditions, indicating that exposure to an obesogenic diet modifies the hippocampal inflammatory environment. Collectively, these findings suggest that early-life exposure to an obesogenic diet disrupts hippocampal homeostasis through coordinated inflammatory and dopaminergic mechanisms that may compromise memory-related plasticity. Cognitive stimulation without the need of exercise or complex housing arrangements may encourage resilience by preserving hippocampal function and limiting the neurobiological consequences of diet-induced obesity.

Disclosures: S. Hernández-Ramírez: None. **E. Cordero:** None. **K.R. Guzman-Ramos:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.14/KK38

Topic: I.08. Learning and Memory

Support: NIHDDK grant DK118000
NIHDDK grant DK140275

Title: Transcriptomic profiling of hippocampal neurons and astrocytes of Western diet-induced cognitive impaired mice

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Abstract: Consuming a diet high in saturated fats and added sugars, termed a Western diet (WD), negatively impacts hippocampal-dependent learning and memory through unclear mechanisms. Our objective was to identify potential mechanisms driving WD-induced hippocampal dysfunction. We hypothesized that a WD differentially impacts hippocampal gene expression in a cell-type specific manner. C57BL/6J male and female mice were maintained on a WD (n=14) or standard chow (n=16) for 8 weeks which impaired hippocampal-dependent spatial memory performance in the Novel Location Recognition task (one sample t-test against chance levels). We extracted hippocampal tissue and isolated Thy1-expressing (enriched in glutamatergic neurons) and Hepacam-expressing (enriched in astrocytes) cells for RNA sequencing, differential gene expression analyses, and functional enrichment pathways analyses (n=8/group). Statistical significance for gene expression data was defined as |log2Fold-Change|>1 and a Benjamini-Hochberg adjusted p value<0.05. Results revealed that the majority of differentially expressed genes were downregulated by a WD in both neurons and astrocytes. In neurons, pathways related to complex I of the mitochondrial electron transport system were robustly downregulated by a WD, and this corresponded to a downregulation of all 13 protein-encoding genes found on mitochondrial DNA. Upregulated pathways were related to neuropeptide signaling, ligand-receptor interactions, and presynpatic communication. In astrocytes, pathways related to inflammation and immune systems were downregulated while pathways related to cytoskeletal and microtubule organization were upregulated. These findings suggest that a WD impacts gene expression in the hippocampus and provides valuable direction for researchers investigating mechanisms contributing to WD-induced cognitive dysfunction.

Disclosures: L. Loera-Lopez: None. **E. Noble:** None.

Poster

PSTR076: Gene Regulation and Molecular Switches in Learning and Memory

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR076.15/KK39

Topic: I.08. Learning and Memory

Support: U.S.-Israel Binational Science Foundation

Title: EphB2 Acts as a Molecular Switch Regulating Fear Memory Stabilization and Destabilization

Authors: *B. POPIK[1], A. FARHAT[1], K. D. SRIKANTH[2], M. B. DALVA[2], R. LAMPRECHT[1];
[1]Univ. of Haifa, Haifa, Israel; [2]Neurosci., Tulane Univ., New Orleans, LA

Abstract: Memory traces must be stabilized after learning to support long-term retention, yet following retrieval they can become transiently unstable, allowing new information to be

incorporated. The molecular mechanisms that coordinate these opposing processes and ensure that only reactivated memories are updated remain to be elucidated. Here, we identify the receptor tyrosine kinase EphB2 as a bidirectional regulator of fear memory stability in excitatory neurons of the basolateral amygdala, acting through distinct domain-specific pathways. Conditional deletion of EphB2 impaired long-term fear memory formation while sparing short-term memory, demonstrating its essential role in post-learning memory stabilization. In addition, EphB2 was required for retrieval-induced memory destabilization. These results reveal a dual role for EphB2 in both memory stabilization and destabilization. Consistent with this, optogenetic stimulation of a photoactivatable form of EphB2 (optoEphB2) during memory retrieval was sufficient to induce memory destabilization and attenuate fear memory expression. This effect was absent in mice expressing a kinase-inactive optoEphB2, indicating that EphB2 kinase activity is required for memory destabilization. Further mechanistic analyses revealed that the extracellular tyrosine residue Y504, which mediates NMDA receptor recruitment, is selectively required for memory destabilization but dispensable for stabilization. Accordingly, mice carrying a conditional Y504F mutation in excitatory neurons exhibit normal long-term memory formation but fail to destabilize memories following retrieval. Together, these findings establish EphB2 as a molecular switch that governs both stabilization and destabilization of fear memories based on prior experience.

Disclosures: B. Popik: None. **A. Farhat:** None. **K.D. Srikanth:** None. **M.B. Dalva:** None. **R. Lamprecht:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.01/KK40

Topic: I.08. Learning and Memory

Title: Distinct Mushroom Body Networks Gate Spatial Threat Avoidance in Drosophila

Authors: *Y. GU[1], Y. HIRANO[2];
[1]The Hong Kong Univ. of Sci. and Technol., Hong Kong, China; [2]The Hong Kong Univ. of Sci. and Technol., Hong Kong, Hong Kong

Abstract: Animals must learn the spatial locations of danger to survive. While the Drosophila mushroom body (MB) is essential for olfactory and visual memory, whether flies can use proprioceptive cues to navigate a complex environment—and the underlying neural circuits—remains unknown. We developed an operant map learning paradigm in a four-zone arena under complete darkness with infrared backlighting, where one zone delivers electric shocks, to investigate the neuronal mechanisms driving spatial decision-making. Using genetic and optogenetic manipulations, we silenced or activated specific MB populations while monitoring free-moving avoidance behavior.

Our initial results suggest that flies can exhibit spatial learning, showing a reduction in entries into the shock zone. This spatial discrimination appears to depend on intact dopaminergic signaling from both PPL and PAM subsets, alongside functional MB α'/β' lobes; silencing these populations substantially reduced zone avoidance. Furthermore, we identified potential distinct roles for specific mushroom body output neurons (MBONs) in memory acquisition versus behavioral execution. MBON-γ1pedc, traditionally implicated in classical shock memory, appeared preferentially involved in avoidance execution. Optogenetic repression of this neuron at the shock zone entry point—but not within the zone itself—promoted avoidance. Conversely, optogenetic activation at the entry point led to an increase in entries into the shock zone, overriding shock aversiveness. This points to a potential role for this circuit element as a predictive threat signal rather than encoding the shock experience per se. In contrast, optogenetic silencing of α'/β'm Kenyon cells or their downstream MBONs at the entry point disrupted memory acquisition while leaving memory retrieval largely intact after normal learning. To directly capture how neural activity relates to memory or decisions, we are currently developing a real-time calcium imaging system for freely moving flies.
Together, our current findings suggest that Drosophila can form proprioceptive-based spatial memories relying on compartmentalized MB circuits. This provides a framework for a predictive gating mechanism where distinct MBON pathways may independently process entry decisions versus memory formation to guide adaptive behavior in complex environments.

Disclosures: Y. Gu: None. **Y. Hirano:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.02/KK41

Topic: I.08. Learning and Memory

Support: NIH Grant R01NS121220

Title: Large-scale voltage imaging reveals Aplysia's isolated pedal ganglion is sufficient for non-associative learning during fictive locomotion

Authors: D. S. KOVALEV[1], *V. K. MISTRY[1], E. S. HILL[2], **W. N. FROST**[2];
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Abstract: In small invertebrate networks, rhythmic motor programs are often mediated by neurons spread across various ganglia. In the sea slug *Aplysia californica*, multiple behavioral circuits have been described that can operate and modulate themselves within a single ganglion. But is this the case with its gallop/crawl escape locomotion? While the efferent neurons are in the pedal ganglion, previous studies have identified critical modulatory command-like neurons in

the cerebral ganglion. However, prior work has also shown that a rudimentary motor program (MP) can be elicited in fully-isolated, single pedal ganglion (Jahan-Parwar & Fredman, 1980), but with fewer cycles and less intense bursts. More recently, Wang et al., (2023) provided strong evidence that a portion of the MP's central pattern generator is located in the pedal ganglia. We recently showed sensitization and habituation learning in the locomotion MP with the ring ganglia connected, but didn't address where that learning might reside in the nervous system. Here we investigated the ability of a fully isolated pedal ganglion to both generate the locomotion MP and also undergo nonassociative learning. The ring ganglia of middle-aged adult *Aplysia* were excised and neuronal activity was recorded in the pedal ganglion using voltage-sensitive dye (VSD), with fictive locomotion elicited via an ipsilateral pedal nerve stimulus. After confirmation of a MP in the pedal ganglion, we then severed and removed all other ganglia, leaving a solitary pedal ganglion that rested for 1 hour before an identical recording & stimulus delivery. We recapitulated the prior findings, and also found that these MPs retained gallop and crawl phases, along with the burst phase shifts present in connected ganglia that underlie the rolling pedal wave locomotion. This was confirmed with VSD-free intracellular recordings. A same-site non-associative learning protocol was implemented in these isolated pedal ganglia (5 identical stimuli delivered with a 10 min ISI), and we observed both sensitization and habituation of the MP (measured by changes in average neuronal spiking rate and neuronal allocation), as in connected ganglia recordings. Thus, an isolated pedal ganglion is sufficient to mediate non-associative learning. These findings demonstrate that while the other ganglia provide relevant modulatory inputs for locomotion, the pedal ganglion is capable of self-modulation for non-associative learning. This reframes the field's understanding of the locomotion network, and suggests redundant modulatory capacities across the ring ganglia, a potential protective network property to preserve locomotor capacity into old age.

Disclosures: D.S. Kovalev: None. **V.K. Mistry:** None. **E.S. Hill:** None. **W.N. Frost:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

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Topic: I.08. Learning and Memory

Support: NIH Grant 2R15MH107892-03 to I.C.-J. and R.C.-J.

Title: How Does Extended Training Produce More Durable Memories? Clues from Long-Term Sensitization in Aplysia

Authors: E. CARON, C. MCFAUL, *R. J. CALIN-JAGEMAN, I. E. CALIN-JAGEMAN; Neurosci. Program, Dominican Univ., River Forest, IL

Abstract: Most long-term memories become less accessible over time, but extended training can produce long-term memories that are remarkably durable. This has been well-documented in *Aplysia californica* where "standard" long-term sensitization training (4 painful shocks delivered in one session) produces a transcription-dependent long-term memory that nevertheless fades within ~1 week, but "enhanced" training (4 painful shocks delivered on 4 consecutive days) produces sensitization that is stably expressed for at least 2 weeks. Here we explored the molecular basis of this training effect by conducting transcriptional gene expression profiling from pleural ganglia harvested 1 day after standard or enhanced training (N = 16 animals per group, pooled to create 8 paired samples per group for transcriptional analysis). As expected, enhanced training produced a notably stronger initial sensitization memory compared to standard training (245% increase in reflex duration vs. 170% increase in reflex duration). RNA-Seq identified 52 transcripts clearly regulated in both conditions (statistically significant change of more than 10% with correction for 5% FDR), 23 clearly regulated after standard training and 177 regulated after enhanced training, but none of the genes that differed in significance status showed a statistically-significant difference between conditions. Despite having more flagged transcripts, the overall pattern of gene-expression changes was somewhat *weaker* following enhanced training, with an average reduction of regulation of about 20%. Comparison of untrained samples from both conditions did not show any clear induction of "bleed-over" of expression changes on the untrained side due to enhanced training. Comparing these results to a previous microarray experiment of the same design showed that RNA-seq's higher dynamic range yields lower power, and that even our relatively large sample size was barely adequate for paired comparisons. Overall, our results do not provide any qualitative/clear transcriptional differences in the initial regulation evoked by standard versus enhanced training.

Disclosures: E. Caron: None. **C. McFaul:** None. **R.J. Calin-Jageman:** None. **I.E. Calin-Jageman:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.04/KK43

Topic: I.08. Learning and Memory

Support: McNair Scholars Program, P031A240179

Title: Conditioned Place Preference Shifts in Planarian Flatworms

Authors: *V. FLORES[1], C. G. REICH[2];
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Abstract: A growing body of evidence suggests that planarian flatworms (Dugesia dorotocephala) possess a functional endocannabinoid system, yet its role in reward learning

remains unclear. The present study tested whether sucrose could produce a conditioned place preference (CPP) shift in D. dorotocephala, establishing a behavioral paradigm for later examination of CB1 receptor modulation using WIN-55,212-2 and AM251. Planarians (n = 39) were acclimated in spring water and tested in a biased half-light/half-shaded Petri dish, using their natural photophobia to define the light-exposed side as the non-preferred context. Each worm completed four phases: 5 min habituation, 5 min pre-conditioning preference test, 30 min conditioning in either spring water or 5% sucrose, and a 5 min post-conditioning preference test. Time spent in the light-exposed and shaded contexts was converted into a CPP index, and change in CPP was calculated as post-conditioning CPP minus pre-conditioning CPP. A 2 (Group: control, sucrose) × 2 (Conditioning Phase: pre, post) mixed-model ANOVA found no significant Group × Phase interaction, indicating that sucrose did not produce a statistically reliable CPP shift relative to water controls. Both groups, however, spent significantly more time in the initially non-preferred light context after conditioning, $F(1,37) = 9.78$, $p = .003$. Between-group differences in CPP approached but did not reach significance, $F(1,37) = 3.99$, $p = .053$. An independent-samples t-test on change in CPP likewise found no significant difference between groups, $t(37) = -1.67$, $p = .103$, $d = -.54$. These preliminary findings suggest that sucrose may produce a modest place preference shift, but high variability in photophobia, exploratory behavior, and wall-hugging likely obscured group-specific effects. Future procedural refinements will aim to reduce within-subject variability to establish true CPP shifts. Dimethyl sulfoxide (DMSO) concentrations (0, 0.1, 1%) were compared against spring water to test for motility to make sure CB1 drug solutions cause no significant behavioral effects attributed to velocity. Data analysis is underway. Future work will test CB1R activation/antagonism on CPP expression.

Disclosures: V. Flores: None. **C.G. Reich:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.05/KK44

Topic: I.08. Learning and Memory

Title: Memory trace shifting between ensembles via structural dynamics mediates active forgetting in Drosophila

Authors: *N. HUANG[1], J. ZHOU[1], Y. ZHONG[2];
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Abstract: Background: Forgetting is increasingly recognized as an active, adaptive process essential for behavioral flexibility, yet its underlying mechanisms at the cellular and synaptic levels remain elusive. **Objective:** This study aims to investigated the structural synaptic dynamics mediating two distinct forms of forgetting in *Drosophila*: natural memory decay and rapid memory updating during reversal learning. **Methods:** We combined aversive olfactory

conditioning with in vivo ACh3.0 imaging to monitor functional memory traces and the STaR system to track endogenous Bruchpilot for active zone (AZ) structural changes across γ Kenyon cell compartments. Candidate pathways were validated across behavioral, functional, and structural levels. **Results:** For natural memory decay, we found that forgetting is promoted by shifting memory traces between distinct synaptic ensembles: an initial presynaptic depression trace in γ1 shifts over time to γ4 as presynaptic potentiation, which dissipates concurrently with behavioral memory loss. This trace transfer is initiated by Rac1/Dia-dependent addition of AZs, whereas subsequent memory erasure is driven by Ephrin-dependent AZ elimination. Consequently, preventing this shift preserves the γ1 memory trace for over a day without forgetting. In contrast, we discovered that the original memory trace involved in reversal learning resides in a fundamentally different compartment compared to that of a standard two-session massed training. Although reversal learning triggers a similar sequence of presynaptic AZ structural dynamics, it operates on a much faster timescale, featuring a transient AZ increase immediately upon memory updating followed by prompt elimination. Critically, this rapid regulation is mediated by Neurexin-1, defining a context-specific pathway distinct from Dia-dependent decay. **Conclusions:** We conclude that parallel synaptic ensembles encode memory traces with distinct forgetting characteristics. Forgetting involves dynamic trace transfer between these ensembles, governed by specific molecular pathways (Dia vs. Neurexin-1) that dictate the speed and context of memory erasure.

Disclosures: N. Huang: None. **J. zhou:** None. **Y. Zhong:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.06/KK45

Topic: I.08. Learning and Memory

Title: Functional imaging of competing memory traces reveals that spontaneous recovery is driven by active forgetting of a distinct extinction-induced aversive memory

Authors: *J. ZHOU;
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Abstract: Extinguished behaviors often return spontaneously over time, posing major challenges for treating disorders such as addiction, yet the circuit-level mechanisms remain elusive. Here, using functional imaging and behavioral analyses in Drosophila, we uncover that this spontaneous recovery arises from active competition between memories. Reward conditioning establishes a stable appetitive memory, while subsequent extinction training does not erase it but instead forms a separate, extinction-induced aversive memory. This aversive trace is qualitatively distinct from a typical conditioned punishment memory, as it is intrinsically unstable and prone to active decay. We find that the extinction-engendered aversive memory

undergoes active forgetting specifically through the Rac1/Dia signaling pathway, thereby releasing the original reward memory from inhibition and leading to spontaneous recovery. Manipulating Rac1 activity has no effect on the initial sugar-reward memory or the immediate effectiveness of extinction, but it bidirectionally regulates the decay of extinction memory and thus the degree of recovery. Functional imaging directly visualizes the neural representation of this competing aversive trace and its subsequent decay, corroborating that extinction is encoded as an aversive-like experience. Furthermore, genetic and pharmacological disruption of the formin Dia, a downstream effector of Rac1, selectively blocks spontaneous recovery, stabilizing both behavioral performance and the corresponding physiological memory traces. Together, these results demonstrate that spontaneous recovery is not a passive fade of extinction, but an active process of memory competition, in which the active forgetting of a unique, extinction-born aversive memory allows the original reward memory to re-emerge.

Disclosures: J. zhou: None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.07/KK46

Topic: I.08. Learning and Memory

Title: Neural mechanisms for learning multiple cue-to-reward intervals

Authors: *I. PISOKAS[1], D. B. BUSHEY[2], S. ROMANI[2], Y. ASO[3];
[1]Janelia Res. Campus, HHMI, Ashurn, VA; [2]HHMI Janelia Res. Campus, Ashburn, VA; [3]Aso Lab., Janelia Res. Campus, Ashburn, VA

Abstract: Learning temporal relationships between sensory cues and subsequent reward or punishment enables animals to predict future outcomes and select appropriate anticipatory actions. In many situations, not only the identity of the predicted outcome but also its timing is critical; anticipatory actions expressed too early or too late may be ineffective or detrimental. Although interval timing is essential for adaptive behavior, the neural mechanisms that allow animals to learn minute-long cue-to-reward intervals, associate different sensory cues with distinct reward latencies, and organize their behavior according to expected reward timing remain poorly understood.
We show that *Drosophila melanogaster* can learn to associate different odors with distinct odor-to-reward intervals, including intervals longer than one minute. Using optogenetics to precisely control reward timing, we trained flies to associate one odor with immediate reward and another with future reward (trace conditioning), for example 60 seconds after odor onset. During testing, when both odors were presented simultaneously at separate locations, flies first approached the odor associated with immediate reward and then navigated to the odor associated with future reward, arriving near the expected reward time. Thus, flies were able to organize the sequence of

their actions in anticipation of reward delivery.
We next used cell-type-specific optogenetic activation of dopaminergic neurons to identify neural substrates supporting this temporal interval learning. Conditioned responses were partially recapitulated by targeting dopaminergic neurons projecting to individual mushroom body compartments. Dopaminergic neurons projecting to mushroom body compartments γ4 and γ5 were most effective at inducing trace-conditioning memory. These experiments revealed that cue-reward temporal contingency differentially modifies synaptic strengths across multiple mushroom body compartments, producing a population code for cue-to-reward intervals in mushroom body output neuron activity.
Based on these findings, we propose a mechanistic model in which mushroom body compartments, through compartment-specific plasticity rules with distinct temporal sensitivities, modulate the expression of different behavioral competencies. These compartment-specific changes in mushroom body output and behavioral modulation enable flies to select and sequence their actions according to the expected timing of reward.

Disclosures: I. Pisokas: None. **D.B. Bushey:** None. **S. Romani:** None. **Y. Aso:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.08/KK47

Topic: I.08. Learning and Memory

Support: PAPIIT IN225925
PAPIME PE305125

Title: Novel space recognition in octopus using a Y maze

Authors: *N. TRUJILLO GUTIÉRREZ[1], F. SÁNCHEZ-FLORES[3], H. SANCHEZ-CASTILLO[2];
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Abstract: Cephalopods have been the focus of numerous studies on cognitive processes, such as learning and memory tasks. Due to its similarities in cognition but differences in nervous system organization and arrangement when it's compared to mammals and other vertebrates. In our laboratory, O. maya has been successfully proved to recognize and discriminate objects with different shapes (novel object recognition paradigm), however when they are juvenile (up to 2 months old), they are unable to complete the task, in contrast to adult subjects. The main goal of this research was to implement the recognition paradigm with a novel space instead of an object. To achieve this goal, we used the substrate, in which the animals are housed, as a key indicator for recognition. Subjects were randomly distributed to two different substrates: a rocky coarse,

dark colored substrate and a finer light-colored sandy substrate. To evaluate the memory processes, we use both substrates in the Y Maze Paradigm. The protocol was divided into two phases: 1. Habituation: In this phase, the subjects were delivered to the central arm of the y maze (without substrate), the animals were free to explore the arm containing the familiar substrate (the other remains closed), for 15 minutes (rocky or sand, counterbalanced). Once the habituation phase ended, phase two began, the recognition phase. Here, the subjects were free to explore both arms, one arm containing the familiar substrate and the other with the novel one. We measure the time expended in both arms.The obtained results show a clear preference for rocky dark substrates independently of habituation stimuli, but there is less arm exploration to the habituated substrate, suggesting that octopuses can recognize previously explored spaces based on tactile stimuli. Further studies with other substrates must be put to the test.

Disclosures: N. Trujillo Gutiérrez: None. **F. Sánchez-Flores:** None. **H. Sanchez-Castillo:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.09/KK48

Topic: I.08. Learning and Memory

Support: NSF Grant IOS-2322317

Title: Plasticity Induced by Coactivation of Distinct Sensory Circuits Modulates Stimulus-Elicited Locomotion in C. elegans

Authors: M. ARSLAN, B. STROH, A. KELLEY-HENROID, C. ROBISON, J. D. STEELE, K. H. NGUYEN, *J. K. ROSE;
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Abstract: Neurons experience multiple stimulus inputs at any one time; how these signals are reconciled by neurons to drive a final behavioral output was explored. The present study employed the *C. elegans* model system due to its simple, well-described nervous system, whereby neuron circuits that connect stimulus inputs to behavioral outputs are known. Based on the known neuron connectivity, we tested if repeated pairing of two stimulus inputs that drive opposing locomotor responses altered the response to a single stimulus. To test this, worms received 5 pairings of blue light exposure (to drive forward locomotion) with mechanical tap stimulation (to drive backward locomotion), at a 60 s interstimulus interval. Locomotor responses to tap were measured at one- and ten-minute retention intervals. Naive worms were shown to typically respond to tap with a backward locomotor response; however, worms that received blue light + tap pairings responded to tap with ‘paused’ locomotor behavior and decreased forward and backward locomotor responses at both one and ten minutes after pairings.

This behavioral outcome of repeated stimulus pairing was different from when worms received only 5 taps or 5 blue light presentations at a 60 s interstimulus interval. A group that received 5 blue light presentations followed by a tap stimulus one or ten minutes later showed a moderate decrease in reversal responses to tap, suggesting the potential for crosstalk between circuits. Current work is exploring how coactivation of distinct circuits that drive the same locomotor response may alter response behaviors. This will allow for comparison between behavioral plasticity resulting from pairing opposing response circuits versus pairing converging stimulus circuits that drive the same locomotor response, to help discern how neural circuits integrate multiple signals to tune behavioral output.

Disclosures: M. Arslan: None. **B. Stroh:** None. **A. Kelley-Henroid:** None. **C. Robison:** None. **J.D. Steele:** None. **K.H. Nguyen:** None. **J.K. Rose:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

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Topic: I.08. Learning and Memory

Support: NIAAA R01AA024434
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NIAAA NRSA F32029595
NIDA R01DA058947
Brown University Dean's Postdoctoral Diversity Fellowship in Biology and Medicine

Title: Characterizing Choice Behavior in Drosophila Olfactory Classical Conditioning

Authors: *S. G. STEA[1], T. M. BROWN[2], R. ORAMAS[2], R. AZANCHI[2], J. HERNANDEZ[2], K. R. KAUN[2];
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Abstract: *Drosophila melanogaster* is a powerful model organism to understand the neural and molecular mechanisms underlying learning and memory. However, memory is usually studied by assessing choice behavior at only one point in time in *Drosophila*, which limits our understanding of how flies respond to a learned cue. We developed a **simple open-field style assay** that records the continuous behavioral dynamics of flies as they form preferences between two competing olfactory stimuli. We trained flies to associate odors with either a reward (sucrose) or punishment (electric shock) and found that within 30 seconds, flies learned to approach the sugar-associated odor and avoid the shock-associated odor. Their collective behavior dynamics suggest the flies became more decisive over time; they traveled more on the preferred side, stayed closer to the source of the preferred cue, made more stops there, and

consistently turned away from alternative cue. We confirmed these results by showing that a learning-deficient mutant strain displayed no choice behavior. This assay provides enhanced resolution for understanding decision-making as a continuous, dynamic process in *Drosophila*.

Disclosures: S.G. Stea: None. **T.M. Brown:** None. **R. Oramas:** None. **R. Azanchi:** None. **J. Hernandez:** None. **K.R. Kaun:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.11/KK50

Topic: I.08. Learning and Memory

Support: German Research Foundation (DFG) Grant 365082554 (FOR 2705)

Title: Confinement of cAMP signals by the phosphodiesterase dunce in axonal boutons of Drosophila mushroom body neurons - implications for associative learning

Authors: S. DEIMEL, L. EPPLE, ***A. FIALA**;
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Abstract: A central question in neuroscience concerns how synaptic plasticity underlying learning and memory can be confined to specific synapses within a neuron while leaving neighboring synapses unaffected. In *Drosophila melanogaster*, associative olfactory learning induces synaptic plasticity in the mushroom body γ-lobe Kenyon cells, restricted to specific axonal compartments (γ1-γ2 for aversive, γ4-γ5 for appetitive olfactory learning). The second messenger cAMP plays a key role in synaptic plasticity, yet its high diffusion coefficient poses the question of how its spread across axonal compartments is prevented. We hypothesized that the cAMP phosphodiesterase *dunce* (PDE4 family) acts as a functional barrier that confines cAMP signals to specific axonal boutons of distinct axonal compartments. Using *in vivo* two-photon cAMP imaging with the genetically encoded sensor G-FlaMP1, expressed in individual γ-lobe Kenyon cells via the MARCM technique, we monitored punishment-induced cAMP dynamics at the resolution of single axonal boutons and inter-bouton sections across all five γ-lobe compartments. In wildtype flies, electric shock-induced cAMP increases were strongly confined to compartments γ1-γ3 and were significantly higher in axonal boutons than in inter-bouton sections. RNAi-mediated knockdown of *dunce* specifically in γ-lobe Kenyon cells abolished this compartmentalization: cAMP transients spread more into the reward-associated γ5 compartment and the difference between boutons and inter-bouton sections was largely decreased. Knockdown of *dunce* in the γ-lobes of the mushroom body also impaired aversive associative learning behavior. To determine the subcellular localization of *dunce*, we developed a novel CRISPR/Cas9-based strategy to restrict expression of endogenous GFP-tagged *dunce* to individual Kenyon cells. Super-resolution STED microscopy revealed that *dunce* is

predominantly localized to axonal boutons and concentrated at their periphery, suggesting a structural basis for its role as a diffusion barrier. These results suggest that *dunce* acts as a nanoscale enzymatic barrier that restricts cAMP diffusion to individual axonal boutons, thereby confining memory engrams to appropriate synaptic boutons and axonal compartments.
Keywords: cAMP signaling, phosphodiesterase, dunce, mushroom body, *Drosophila melanogaster*, synaptic plasticity, learning and memory, STED microscopy, optical imaging, axonal compartmentalization

Disclosures: S. Deimel: None. **L. Epple:** None. **A. Fiala:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.12/KK51

Topic: I.08. Learning and Memory

Support: NIH Grant NS101356
NIH Grant NS118606

Title: Motor priming is associated with widespread recruitment into neural ensembles and more rapid ensemble transitions

Authors: *A. GUPTA[1], C. NEVEU[2], E. C. CROPPER[3], J. H. BYRNE[4];
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Abstract: Repetition priming is a ubiquitous form of implicit learning in which repetition leads to increased performance. To better elucidate changes in neural activity that mediate priming, we investigated egestive priming of feeding behavior in the tractable model organism *Aplysia californica*. Egestive priming was induced in an isolated cerebral and buccal ganglia preparation, and the activities of numerous neurons, some well-characterized and others previously uncharacterized, were recorded using voltage-sensitive dye (VSD) imaging. The high-dimensional VSD data were subjected to tensor component analysis, which isolated and characterized three neuronal ensembles with distinct spatial and temporal domains. The activities of these ensembles corresponded to three motor phases: radula protraction, early retraction, and late retraction. Priming resulted in repetition enhancement characterized by increased neural activity during early retraction (i.e., ensemble-specific gain modulation), as well as a more rapid transition into the late retraction ensemble. In addition, priming recruited previously inactive neurons into the protraction and early retraction ensembles. These results indicate that priming-induced neural plasticity is multifaceted, operating across multiple axes of plasticity (i.e., gain

modulation, recruitment, and more rapid ensemble transitions), and that each axis modifies specific subsets of ensembles.

Disclosures: A. Gupta: None. **C. Neveu:** None. **E.C. Cropper:** None. **J.H. Byrne:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.13/KK52

Topic: I.08. Learning and Memory

Support: NIH Grant NS101356

Title: Operant reward learning in Aplysia regulates long-term excitability by reducing expression of a metabotropic glutamate receptor.

Authors: *C. L. NEVEU[1], Y. MOMOHARA[2], B. L. RAVEENDRA[3], Y. ZHAO[3], E. MOCCI[4], S. A. AMENT[6], A. MAHURKAR[5], T. W. ABRAMS[7], S. V. PUTHANVEETTIL[8], J. H. BYRNE[9];
[1]UTHealth, Houston, TX; [2]Neurobio. and Anat., McGovern Med. Sch. at The Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX; [3]The Scripps Res. Institute, Scripps Florida, Jupiter, FL; [4]Univ. of Maryland Sch. of Med., Baltimore,, MD; [5]Univ. of Maryland Sch. of Med., Baltimore, MD; [6]Dept. of Psychiatry and Inst. for Genome Sci., U Maryland Sch. of Med., Baltimore, MD; [7]Pharmacol., U of Maryland Med. Sch., Baltimore, MD; [8]Neurosci., UF Scripps Biomed. Res., Jupiter, FL; [9]Dept. of Neurobio. and Anat., McGovern Med. Sch. at UTHealth Houston, Houston, TX

Abstract: Although long-term changes in intrinsic excitability are a cellular hallmark of learning and memory, the molecular machinery underlying changes in excitability remains poorly understood. We leveraged the technical advantages of *Aplysia californica* to investigate the molecular mechanism by which operant reward learning modifies the intrinsic excitability of motor neuron B9, a key neuron involved in feeding behavior. Excitability was assessed before, immediately after, and 24 h after an *in vitro* analog of operant reward learning, which consisted of a contingent group that received stimulation of the esophageal nerve containing afferent dopaminergic processes immediately following ingestion motor programs (contingent reinforcement) and a yoke preparation that received the same nerve stimulation irrespective of motor programs. Conditioning led to a significant increase in B9 excitability immediately and 24 h after contingent reinforcement training compared to yoke training. Single-cell RNAseq analysis indicated that reinforcement reduced the expression of a metabotropic glutamate receptor ($ApmGluR_A$) in B9 24 h after training (see accompanying abstract). We hypothesized that $ApmGluR_A$ decreases B9 excitability, leading to increased B9 excitability following operant conditioning. Consistent with this hypothesis, an mGluR agonist significantly decreased B9

excitability; however, the agonist did not significantly decrease B9 excitability in the presence of a $G_{aq/11}$ inhibitor. Knocking down expression of $ApmGluR_A$ by injecting an oligonucleotide specific for this gene into B9 suppressed the mGluR agonist-induced decrease in excitability, compared to the control oligonucleotide. These results suggest that operant conditioning-induces short- and long-term increases neuronal excitability are mediated by a novel mechanism involving reduction of the expression of a metabotropic glutamate receptor in a $G_{aq/11}$-dependent pathway.

Disclosures: C.L. Neveu: None. **Y. Momohara:** None. **B.L. Raveendra:** None. **Y. Zhao:** None. **E. Mocci:** None. **S.A. Ament:** None. **A. Mahurkar:** None. **T.W. Abrams:** None. **S.V. Puthanveettil:** None. **J.H. Byrne:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

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Program #/Poster #: PSTR077.14/KK53

Topic: I.08. Learning and Memory

Support: NIH grant NS101356
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Title: Operant conditioning induces persistent neuron specific transcriptional programs in the Aplysia Feeding Circuit

Authors: B. L. RAVEENDRA[1], C. NEVEU[2], Y. MOMOHARA[3], Y. ZHAO[1], E. MOCCI[4], S. A. AMENT[5], T. W. ABRAMS[6], J. H. BYRNE[7], ***S. V. PUTHANVEETTIL**[8];
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Abstract: Operant Conditioning Induces Persistent Neuron-Specific Transcriptional Programs in the Aplysia Feeding Circuit
Bindu Raveendra, Curtis Neveu, Yuto Momohara, Yibo Zhao, Evelina Mocci, Seth Ament, Anup Mahurkar, Tom Abrams, John Byrne, Sathyanarayanan V Puthanveettil
Although operant conditioning (OC) is a fundamental form of associative learning that shapes adaptive behavior through reinforcement, the molecular mechanisms that support long-term behavioral change remain poorly understood. At the neural circuit level, OC engages reinforcement pathways that couple behavioral outcomes to enduring modifications in neuronal function. While learning-induced transcriptional changes have been documented in several

systems, the long-term, neuron-specific transcriptional programs induced by operant conditioning remain largely unexplored. To address this question, we leveraged the well-characterized feeding circuitry of Aplysia and performed transcriptomic analyses of three identified neurons (B4/5, B6, and B9) known to undergo plasticity during operant conditioning. We hypothesized that operant conditioning induces persistent, neuron-specific transcriptional responses that reflect the distinct functional roles of individual neurons within the reinforcement-learning circuit. To identify long-lasting molecular changes associated with memory storage, we focused on a late time point (24 h post-training). Identified neurons were isolated from contingent (operantly conditioned) and yoked control animals (N = 5-7 neurons per group) and subjected to single-neuron RNA sequencing. Differential expression analyses revealed robust and highly neuron-specific transcriptional responses. B4/5, B9, and B6 neurons exhibited 364, 455, and 606 unique differentially expressed genes (DEGs), respectively, while only 52 DEGs were shared across neuronal populations. These transcriptional changes encompassed genes involved in synaptic signaling, neurotransmitter receptors, ion channel function, intracellular signaling pathways, and protein degradation. The predominance of neuron-specific transcriptional signatures suggests that operant conditioning recruits distinct molecular programs in individual circuit elements despite their participation in a common learned behavior. Together, these findings demonstrate that operant conditioning induces persistent and highly specialized transcriptional remodeling within identified neurons of a reinforcement-learning circuit. These results provide new insight into the molecular mechanisms through which reinforcement shapes long-term behavioral change.

Disclosures: B.L. Raveendra: None. **C. Neveu:** None. **Y. Momohara:** None. **Y. Zhao:** None. **E. Mocci:** None. **S.A. Ament:** None. **T.W. Abrams:** None. **J.H. Byrne:** None. **S.V. Puthanveettil:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

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Program #/Poster #: PSTR077.15/KK54

Topic: I.08. Learning and Memory
NIH grant R01 NS019895
NIH grant NS102490

Title: Differences of only minutes in training intervals lead to profound multiple day differences in persistent activation of kinases and CREBs

Authors: *Y. ZHANG, R.-Y. LIU, P. D. SMOLEN, J. H. BYRNE;
McGovern Med. Sch. of UTHSC At Houston, Houston, TX

Abstract: Learning is associated with rapid activation of multiple protein kinases and transcription factors, but few details are known about their long-term activation dynamics as well

as their sensitivities to different learning protocols. To address this question, we compared three training protocols with distinct effectiveness in inducing long-term synaptic facilitation (LTF) of the *Aplysia* sensorimotor synapse: 1) the five-pulse regular-spaced Standard protocol (S) of serotonin (5-HT) with fixed interstimulus intervals (ISIs) of 20 min; 2) the computationally designed five-pulse irregular-spaced Enhanced protocol (E) with ISIs of 10, 10, 5, 30 min; and 3) the two-pulse protocol (2P) with ISI of 45 min. Among these protocols, E can produce LTF up to 5 d, whereas S and 2P produce LTF lasting less than 2 d. We previously compared the dynamics of four kinases critical for LTF after these protocols: the mitogen-activated protein kinase (MAPK) isoforms ERK and p38 MAPK, protein kinase A (PKA), and p90 ribosomal S6 kinase (RSK). All four kinases showed two waves of increases in activation within 24 h. After S and 2P, all kinase activities returned towards basal level at 24 h, but some remained elevated 24 h after the E protocol. To determine whether these effects persist beyond 24 h, we now measured the activation of kinases 48 h after these protocols. Kinase activities at 48 h were only elevated after the E protocol, including PKA (E: elevated by 24.8 ± 4.7% compared to vehicle-treated control, n = 8; S: 3.1 ± 9.6%, n = 8; 2P: 9.5 ± 4.9%, n = 8), ERK (E: 39.9 ± 10.5%, n = 8; S: 6.2 ± 6.3%, n = 8; 2P: 12.6 ± 9.4%, n = 7), and RSK (E: 36.7 ± 6.2%, n = 9; S: 11.7 ± 12.7%, n = 8; 2P: 5.2 ± 7.3%, n = 7). Consistent with the sustained kinase activation, phosphorylation of the transcription activator CREB1 significantly increased 48 h after E (34.1 ± 11.8%; paired t-test, $t_5 = 2.629$, $p = 0.020$). In contrast, no change was observed in the phosphorylation of the transcription repressor CREB2 at 48 h after E (2.2 ± 5.5%; paired t-test, $t_5 = 0.281$, $p = 0.790$). Notably, the maximal difference in ISIs among these three protocols is only 40 min, and the maximal difference between their total durations is only 35 min. However, these data indicate that differences of minutes in training intervals can drive persistent changes in activation of kinases and CREB1 over multiple days. Thus, small changes in the spacing of training trials can have profound consequences on long-term memory mechanisms. We are developing a computational model to characterize the molecular cascades that explain this sensitivity to ISIs, and will use this model to predict improved training protocols to extend memory duration beyond 5 days.

Disclosures: Y. Zhang: None. **R. Liu:** None. **P.D. Smolen:** None. **J.H. Byrne:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.16/KK55

Topic: I.08. Learning and Memory

Support: NIH Grant 1 R01 NS 121904-01
Howard Hughes Medical Institute
EMBO Long-Term Fellowship (ALTF 160-2014), Marie Curie Actions, European Commission
Mohapatra Fellowship in Vision Research at The Rockefeller University

Title: Dopamine neurons report a reward-timing error in the Drosophila mushroom body

Authors: *E. DIAS-FERREIRA, G. MAIMON;
Lab. of Integrative Brain Function and Howard Hughes Med. Institute, The Rockefeller Univ., New York, NY

Abstract: Learning theories propose that violations of reward expectation generate teaching signals that alter future actions. Central to such learning processes is predicting reward timing so as to generate teaching (error) signals when temporal expectations are violated. The *Drosophila* mushroom body provides a small, genetically accessible circuit with identified connectivity in which one can test for the existence of reward-timing error signals and probe their implementation. We first describe a simple, head-fixed visual conditioning paradigm in which a visual-motion stimulus predicts the impending arrival of a sugar drop. Flies report reward expectation in this paradigm through anticipatory proboscis extension movements in response to the visual-motion stimulus. This task enables trial-by-trial measurement of appetitive learning across hundreds of trials. We show that conditioning in this task requires the activity of γd Kenyon cells (KCs), a small population of visually sensitive neurons that innervate five of the fifteen mushroom body compartments. When separate groups of flies were trained to expect reward at distinct post-visual-motion intervals (10 s or 20 s), we observed a rise in dopaminergic activity in the γ2 compartment that peaked near the expected time of reward. Closer analysis revealed that calcium transients in γ2α′1 dopamine neurons and dopaminergic signals measured at γd KC axons increased after each proboscis extension. Remarkably, response amplitude scaled monotonically with the sequential order of proboscis extensions (rather than just elapsed time). Progressively increasing γ2 dopaminergic responses with each proboscis extension predicted progressively weaker conditioned responses on the subsequent trial. These results reveal a reward-timing error signal, expressed in a single, identified, dopamine neuron within the mushroom body, that links dopaminergic activity to trial-by-trial behavioural adaptation, demonstrating temporal computations consistent with reward-prediction error signals in an experimentally tractable circuit.

Disclosures: E. Dias-Ferreira: None. **G. Maimon:** None.

Poster

PSTR077: Cellular and Circuit Mechanisms of Learning and Memory in Invertebrate Models

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR077.17/KK56

Topic: I.08. Learning and Memory

Title: Insulin tunes system-level STM encoding thresholds and reroutes calcium allocation toward LTM in Drosophila memory

Authors: *M.-C. HSU[1], Y.-M. KUO[1], C. LO[2];
[1]Inst. of Basic Med. Sci., Natl. Cheng Kung Univ. Col. of Med., Tainan, Taiwan; [2]Inst. of Systems Neurosci., Natl. Tsing Hua Univ., Hsinchu, Taiwan

Abstract: Neural circuits must balance rapid but labile encoding against slower, stable memory, and inexpensive short-term memory (STM) against costly long-term memory (LTM). How the brain coordinates these rules remains unclear. *Drosophila* offers a tractable model: its mushroom body (MB) contains STM and LTM pathways shaped by dopaminergic neuron (DAN) and MB output neuron (MBON) circuits, with broad insulin receptor (InR) expression. We investigated how insulin/insulin-like signalling (IIS) regulates learning and memory using Pavlovian conditioning, T-maze assays and in vivo imaging under marginal (30 V) or intense (90 V) reinforcement. Across 2,054 flies, we recorded 7,623 traces from MB compartments and insulin-producing cells (IPCs) during training and distinct retrieval phases. IPCs were recruited phasically during training: conditioned stimuli sensitized responses to marginal reinforcement, whereas intense reinforcement produced synergistic activation. Blocking ilp2 secretion lowered the STM threshold, enhancing marginal-reinforcement STM but abolishing intense-reinforcement middle-term memory (MTM) and LTM. Increasing IPC activity during intense-reinforcement acquisition suppressed STM while facilitating MTM and LTM, an ilp2-specific effect. Lobe-specific manipulations revealed partitioned InR functions: InR in the γ and α/β lobes set the acquisition threshold, InR in the α'/β' lobes supported MTM and LTM, and InR in the α/β lobes was required for LTM. CS+ versus CS- calcium bias supported this segregation across STM and LTM compartments. Training-evoked calcium dynamics dissociated the gain code: γ and α/β lobe InR suppressed population noise and regulated response gain, whereas α'/β' lobe InR mainly gated mean response gain. Loss of this gating enhanced weak-reinforcement STM, while InR overexpression primed LTM compartments during marginal training. Simulations revealed STM-like and LTM-like attractor states in MB-MBON-DAN routing dynamics. IIS reshaped MB input toward MBON output, increasing the probability that training shifted the system toward the LTM-like state. Together, these findings suggest that insulin acts online as a tuning filter, biasing training-evoked calcium activity toward the LTM route when an experience is valuable enough to consolidate.

Disclosures: M. Hsu: None. **Y. Kuo:** None. **C. Lo:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.01/KK57

Topic: I.09. Spatial Navigation

Support: NIH Grant MH12928201

Title: Psychedelic control of retrosplenial cortex

Authors: *T. EKINS[1], C. RYBICKI-KLER[2], T. DENG[3], I. JEDRASIAK-CAPE[4], O. J. AHMED[5];
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Abstract: Serotonergic psychedelics produce acute hallucinogenic effects that require activation of serotonin 2A (5-HT_{2A}) receptors. Psychedelics also activate serotonin 2C (5-HT_{2C}) receptors, yet the role of these receptors in their acute effects remains largely unknown. The retrosplenial cortex, a core node of the default mode network important for spatial navigation and memory, is strongly modulated by psychedelics and lacks 5-HT_{2A} receptors, but has the highest density of 5-HT_{2C} receptors in the neocortex. We used whole-cell electrophysiology and pharmacology to investigate the acute impact of serotonergic psychedelics on the intrinsic and synaptic electrophysiology of retrosplenial cortex pyramidal neurons, as well as behavioral assays and machine learning. We find that psychedelics acutely suppress intrinsic excitability of retrosplenial pyramidal neurons while boosting glutamatergic synaptic input. These opposing effects arise through different presynaptic and postsynaptic mechanisms, highlighting the importance of causally disambiguating presynaptic and postsynaptic effects of psychedelics across distinct brain regions.

Disclosures: T. Ekins: None. **C. Rybicki-Kler:** None. **T. Deng:** None. **I. Jedrasiak-Cape:** None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.02/KK58

Topic: I.09. Spatial Navigation

Support: NIH R34NS127101
NIH P50NS12306
NIH R01MH129282

Title: Lightning-Fast Rhythms in the Retrosplenial Cortex

Authors: M. GHOSH, ***O. J. AHMED**;
Univ. of Michigan, Ann Arbor, MI

Abstract: The retrosplenial cortex is important for spatial navigation and memory, and even imagining oneself in the future. Here, we describe the fast rhythms of the retrosplenial cortex and how they are modulated by running speed. We outline the underlying layer-specific neural codes for speed that are shaped by these rhythms across brain states. Together, the work reveals a coding scheme that is implemented by retrosplenial cells and rhythms to structure information processing.

Disclosures: M. Ghosh: None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.03/KK59

Topic: I.09. Spatial Navigation

Support: NIH R01MH129282
NIH R34NS127101
NIH P50NS123067

Title: Linear and angular velocity coding mechanisms in the granular retrosplenial cortex

Authors: *A. MORTAZAVI[1,2], S. KAILASA[1], C. AVILA[3], M. GHOSH[5], O. J. AHMED[4]; [2]Dept. of Neurosurg., [3]Psychology, [4]Dept. of Psychology, [1]Univ. of Michigan, Ann Arbor, MI; [5]Psychology, Univ. of Washington, Seattle, Seattle, WA

Abstract: The granular retrosplenial cortex (RSG) is important for spatial orientation processing. Here, we use both experimental and computational approaches to understand the mechanisms of linear and angular velocity coding in RSG. We first highlight the unique computational capabilities of RSG cells in theoretically encoding angular velocity from their head direction inputs, as well as the persistence of this angular velocity computational code across brain states. Using neuropixel recordings, we then highlight robust encoding of velocity that is both layer- and cell-type-dependent, and assess the impact of angular acceleration versus velocity. Together, the data here shows that neurons in the RSG are ideally positioned to support its orientation computations using cell-type-specific representations of elemental velocity variables.

Disclosures: A. Mortazavi: None. **S. Kailasa:** None. **C. Avila:** None. **M. Ghosh:** None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.04/KK60

Topic: I.09. Spatial Navigation

Support: NIH R01MH129282
NIH R34NS127101
NIH P50NS123067

Title: Psychedelic modulation of the granular retrosplenial cortex in fear extinction

Authors: *E. J. BROUNS[1], T. DENG[5], I. JEDRASIAK-CAPE[2], J. MURRAY[3], N. C. TRONSON[6], O. J. AHMED[4];
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Abstract: Classical, or serotonergic, psychedelics have risen in popularity for the treatment of neuropsychiatric disorders, including depression, substance use disorder, and post-traumatic stress disorder (PTSD), and this benefit is believed to emerge as a result of synaptogenesis and spinogenesis in the prefrontal cortex (PFC). Previous research has established that psychedelics can facilitate fear extinction in preclinical mouse models, but little is known about how other cortical regions involved in fear learning and extinction, such as the retrosplenial cortex, are altered in fear extinction, both with and without psychedelic administration. Here, we demonstrate that a single dose of the classical psychedelic 2,5-Dimethoxy-4-iodoamphetamine (DOI) acutely accelerates fear extinction in male mice, with experiments in females ongoing. Ongoing work is also assessing the impact of DOI vs saline on retrosplenial neuronal intrinsic and synaptic properties, with the goal of uncovering changes in retrosplenial neurons across all experimental timepoints and causally dissecting the reliance of these effects on key serotonergic receptors.

Disclosures: E.J. Brouns: None. **T. Deng:** None. **I. Jedrasiak-Cape:** None. **J. Murray:** None. **N.C. Tronson:** None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

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Program #/Poster #: PSTR078.05/KK61

Topic: I.09. Spatial Navigation

Support: NIH R01MH129282
NIH R34NS127101
NIH P50NS123067

Title: Cellular basis of interhemispheric communication in retrosplenial cortex

Authors: *T. DENG[1], C. RYBICKI-KLER[1], I. JEDRASIAK-CAPE[2], E. BROUNS[3], O. J. AHMED[4];

[1]The Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, ANN ARBOR, MI; [4]Dept. of Psychology, [3]Univ. of Michigan, Ann Arbor, MI

Abstract: The granular retrosplenial cortex (RSG) is important for spatial navigation and memory. Our previous work showed that RSG exhibits two parallel interhemispheric rhythms: gamma rhythms that are in-phase (synchronous) across hemispheres and anti-phase rhythms called "splines" (named after the anti-phase mechanical splines on mechanical gears). Splines are strongly modulated by running speed and rapid eye movement (REM) sleep. However, the cellular circuits mediating these interhemispheric rhythms remain unknown. We hypothesized that interhemispheric coordination could be mediated by contralateral inhibitory or excitatory projections, or potentially both. To test these possibilities, we combined whole-cell patch-clamp recordings with channelrhodopsin-2 (ChR2)-assisted circuit mapping (CRACM), immunohistochemistry, and newly engineered genetically modified mouse lines. We found no evidence of contralateral projections from RSG fast-spiking interneurons, suggesting that while fast-spiking inhibitory neurons play an important ipsilateral role in oscillation generation, they are not carrying this information across hemispheres. Instead, we find that specific subtypes of excitatory neurons provide the major cellular substrate for interhemispheric communication, suggesting that cell-type-specific excitatory circuits underlie coordinated interhemispheric rhythms in RSG and highlighting the unique specializations of the RSG to support information transfer between the left brain and right brain.

Disclosures: T. Deng: None. **C. Rybicki-Kler:** None. **I. Jedrasiak-Cape:** None. **E. Brouns:** None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

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Topic: I.09. Spatial Navigation

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Berger Endowment, G102865/321033

Title: Rapid switching of in-phase and anti-phase interhemispheric rhythms within a single theta cycle: a mechanistic explanation

Authors: *S. KAILASA[1], I. JEDRASIAK-CAPE[2], V. BOOTH[4], O. J. AHMED[3];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Univ. of Michigan, ANN ARBOR, MI; [3]Dept. of

Psychology, Univ. of Michigan, Ann Arbor, MI; [4]Mathematics & Anesthesiol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: In vivo recordings of local field potential (LFP) from granular retrosplenial cortex (RSg) exhibit coexisting gamma (30-80 Hz) and spline (100-160 Hz) oscillations, coupled to distinct phases of the background theta (5-12 Hz) rhythm. Remarkably, bilateral recordings reveal that gamma and splines exhibit divergent interhemispheric phase relationships, with gamma in-phase across hemispheres and splines anti-phase across hemispheres. Motivated to understand these experimental observations, we study a minimal interhemispheric network of next-generation neural mass models, arranged as a pair of delay-coupled excitatory-inhibitory modules. We use techniques from numerical bifurcation theory to mathematically characterize network dynamics in the presence and absence of theta-rhythmic inputs. We demonstrate that experimental observations in RSg may be explained parsimoniously by theta-timescale alternation between oscillations generated by PING- and ING-like mechanisms, with interhemispheric conduction delays enforcing the divergent phase relationships even in presence of rhythmic inputs. Furthermore, we show analytically that a key determinant of whether anti-phase splines and in-phase gamma may coexist is the ratio of the local inhibitory delay to the interhemispheric delay. Thus, our work presents hypotheses for rhythmogenesis in RSg, compares the statistics of experimental recordings to those generated by the model, identifies which model features are crucial to recapitulate the experimentally observed regimes, and constructs phase diagrams for the interhemispheric networks which can inform the design of future optogenetic experiments.

Disclosures: S. Kailasa: None. **I. Jedrasiak-Cape:** None. **V. Booth:** None. **O.J. Ahmed:** None.

Poster

PSTR078: Cortical Circuits and Navigation

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Program #/Poster #: PSTR078.07/KK63

Topic: I.09. Spatial Navigation

Support: (MSIT) IITP-2025-RS-2024-00436857
New Faculty Startup Fund from Seoul National University

Title: Learning-dependent dopamine dynamics in the retrosplenial cortex during flexible goal-directed navigation

Authors: *W. NA, J. KWAG;
Dept. of Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Goal-directed navigation requires animals to transform learned reward information into spatially directed movements, and dopamine signals are proposed to modulate this process through their reward-related signal dynamics. The retrosplenial cortex (RSC) is well positioned to integrate spatial and goal-related information during navigation, as RSC neurons encode task-

relevant variables such as reward-location information and trajectories toward goal locations. However, although dopaminergic inputs to the RSC have been reported, how dopamine dynamics in the RSC are organized during learning and flexible goal-directed navigation remains unclear. Here, we examined whether dopaminergic signaling in the RSC exhibits learning-dependent dynamics during goal-directed navigation. Anterograde and retrograde viral tracing identified a candidate dopaminergic projection from the ventral tegmental area to the RSC. We then monitored RSC dopamine dynamics with GRAB-DA, a genetically encoded dopamine sensor, during an open-field goal-directed navigation task. In this task, mice learned to navigate from a start location to a reward location, followed by reversal learning in which the reward location was changed. Preliminary data revealed an RSC dopamine ramp toward the learned reward location that emerged after task acquisition, was disrupted at reversal onset, and re-emerged with learning of the new reward location. Importantly, ramping activity was observed during reward-directed navigation but not while animals waited at the reward site, suggesting that it is associated with goal-directed approach rather than reward-site occupancy alone. Together, these findings suggest that RSC dopamine contains distinct signals related to goal-directed reward approach, raising the possibility that dopaminergic signaling in the RSC contributes to learning-dependent processes that support goal-directed navigation.

Disclosures: W. Na: None. **J. Kwag:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.08/KK64

Topic: I.09. Spatial Navigation

Title: Anterior cingulate cortex neurons multiplex spatial and temporal signals during patch-leaving foraging in rats

Authors: *Y. DAI[1], J. R. HINMAN[2];
[2]Dept. of Psychology, [1]Univ. of Illinois Urbana-Champaign, Champaign, IL

Abstract: Patch-leaving decision-making requires animals to balance diminishing reward within a current patch against the opportunity cost of exploring alternatives. Prior work implicates the anterior cingulate cortex (ACC) in foraging decisions, but how ACC single units represent patch-leaving decisions in freely moving rats remains unclear. Here, rats performed a two-patch foraging task in which sugar-pellet delivery intervals increased exponentially within a patch and reset after transition to a new patch, while travel cost was manipulated using short and long delays in a transition corridor. Consistent with optimal foraging predictions, rats remained longer in patches when travel cost was high. Guided by c-Fos evidence that ACC is more strongly recruited during patch-leaving than open-field behavior, we recorded more than 1346 single units across 186 sessions from five male rats implanted with 32-channel silicon probes in the left ACC. Using generalized additive models to capture nonlinear relationships between firing rate,

spatial position, elapsed time, and task events, we found heterogeneous but interpretable tuning to patch structure and ongoing behavior. A subset of ACC neurons exhibited spatially restricted firing, with some cells selectively active in the corridor, others preferentially active within individual patch compartments, and others showing elevated activity near entrance-door regions where animals transition between exploitation and travel. These spatially selective responses suggest that ACC neurons represent not only broad task state, such as patch versus corridor, but also finer-grained locations relevant to patch-leaving decisions. In addition to spatial coding, ACC neurons showed temporal organization across multiple behavioral timescales. Some neurons changed firing gradually across the session, whereas others were modulated within individual patch epochs, including activity aligned to pellet-to-pellet intervals. Notably, a subset of neurons showed systematic firing-rate increases or decreases before patch departure, suggesting that ACC activity tracks evolving decision variables before the animal physically leaves the patch. Together, these findings suggest that rat ACC multiplexes spatial context, local reward timing, and temporally evolving pre-departure signals during patch foraging.

Disclosures: Y. Dai: None. **J.R. Hinman:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.09/KK65

Topic: I.09. Spatial Navigation

Title: Frontal cortical representations of navigational goals and planning during dynamic naturalistic foraging

Authors: *N. JOSHUA[1], A. DANIELLY[2], A. MEIR[1], S. NIVINSKY MARGALIT[2], A. FINKELSTEIN[2,1];
[1]Sagol Sch. of Neurosci., [2]Dept. of Neurosci. and Brain Disorders, Gray Fac. of Med. & Hlth. Sci., Tel Aviv Univ., Tel Aviv, Israel

Abstract: Spatial decision-making requires animals to remember where valuable goals are located, update their value based on recent outcomes of interactions with the goal, and combine spatial and value information to guide future choices. However, it remains unknown how goal identity and value are encoded and stored in memory, and how these representations are integrated to support spatial decision-making. This gap is especially apparent in naturalistic foraging, where goals are not always visible or immediately available, and animals must choose between many possible goals.To this end we developed a novel large multi-goal maze in which targets with high reward probabilities were organized into spatial patches. At each epoch, two targets carried the highest reward probability, but their identity changed across the session, requiring rapid relearning. Chronic Neuropixels recordings revealed neurons in the mouse anterior lateral motor cortex (ALM) and orbitofrontal cortex (OFC) that encoded goal identity, patch identity, reward outcome, and patch value independent of the animal's current location.

These signals included both transient and sustained activity patterns. At the population level, neural activity decoded current goal identity, reward magnitude, and reward expectation. Notably, representations of the currently high-value patch persisted even when animals were exploring other patches, indicating that frontal cortical populations maintain latent representations of valuable goals beyond the animal's immediate spatial context.

Disclosures: N. Joshua: None. **A. Danielly:** None. **A. Meir:** None. **S. Nivinsky Margalit:** None. **A. Finkelstein:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.10/LL1

Topic: I.09. Spatial Navigation

Title: Flexible doorway navigation engages door-related coding in anterior cingulate cortex and dorsal subiculum

Authors: Y. DAI[1], R. BURCH[3], G. CHUNG[2], M. RASHED-AL-MAHFUZ[4], ***J. R. HINMAN**[2];
[1]Psychology, [2]Univ. of Illinois Urbana-Champaign, Champaign, IL; [3]Univ. of Illinois, Champaign, Champaign, IL; [4]Univ. of Illinois, Champaign, IL

Abstract: Flexible navigation requires animals to integrate environmental geometry and behavioral affordances, access motivational state, and action contingencies. Doorways are especially informative environmental features because they can serve simultaneously as spatial boundaries, transition points, and behaviorally controllable affordances. However, it remains unclear how the anterior cingulate cortex (ACC) and dorsal subiculum (dSUB) represent doorways when physical access, door mechanics, and behavioral control are systematically dissociated. We recorded neuronal activity using movable, chronic silicon probes implanted in either ACC or dSUB of freely moving rats during a doorway-navigation task. Across recording sessions, the same door locations were manipulated as open gaps, saloon-style doors that the rat could push open from either direction, servo-controlled doors that opened and closed independently of the animal’s behavior, or nosepoke-contingent doors that the rat could open through an operant response. These manipulations were tested in both single-door and dual-door configurations. ACC neurons were modulated by door type and local door-zone occupancy. Some neurons showed increased firing near open gaps, saloon-style doors, or closed/locked doors, whereas others showed suppressed firing near door locations. Additional neurons showed increases or decreases in activity during door-crossing events, suggesting that ACC activity may reflect not only the presence of a doorway but also the animal’s movement through behaviorally meaningful transition points. In nosepoke-contingent sessions, a subset of neurons showed peri-event firing increases around portal actions, consistent with sensitivity to the animal’s control over access. We also observed door-centered egocentric modulation, including neurons whose

activity depended on whether the animal was approaching or leaving a door. In separate recordings from dSUB, neurons also exhibited spatially specific activity related to door crossing, although this door-related specificity appeared less pronounced than in ACC. We additionally observed units with grid-like periodic spatial firing during performance of the same doorway-navigation task. Together, these findings suggest that flexible doorway navigation engages distributed neural representations of doorways across ACC and dorsal subiculum, including signals related to door type, access state, action contingency, door crossing, and self-referenced movement. This task provides a framework for studying how animals organize navigation around behaviorally meaningful environmental transitions.

Disclosures: Y. Dai: None. **R. Burch:** None. **G. Chung:** None. **M. Rashed-Al-Mahfuz:** None. **J.R. Hinman:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.11/LL2

Topic: I.09. Spatial Navigation

Title: Complementary learning dynamics within neocortex and hippocampus

Authors: *Z. KHAN[1], I. VOITOV[1], A. SHAH[1], A. LOSONCZY[1,2], S. FUSI[1];
[1]Columbia Univ., New York City, NY; [2]Peter O'Donnell Jr. Brain Inst., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Efficient learning requires the brain to rapidly encode new experiences while leveraging shared structure across related episodes. Although both area CA1 of the hippocampus and the posterior parietal area of the neocortex (PPC) have been implicated in navigational behavior, it remains unclear how their specialized computations jointly support learning. Here, we used two-photon calcium imaging to record population activity in CA1 and PPC as mice navigated three sequential virtual reality corridors: one familiar environment followed by two novel environments. Each corridor contained a unique cue configuration and a single hidden reward location that the mice rapidly learned following each corridor change, consistent with a meta-learning rule for flexible navigation. PPC neurons exhibited spatial tuning comparable to CA1, but were preferentially anchored to salient cue transitions, whereas CA1 neurons more consistently organized relative to reward location across environments. Next, to capture learning-related changes in population structure within each environment, we developed a representational-geometry metric to quantify how population similarity among positions within each corridor changed with experience, and found both local and distal restructuring of the population code. We find that while CA1 and PPC both rapidly reorganize during learning, they do so at different stages: CA1 first strengthens local similarity and later decorrelates distal positions during exposure to a familiar environment, whereas PPC encodings most strongly decorrelate upon exposure to novelty. Both regions lack this structured modification upon

exposure to a second novel environment, suggesting a physiological limit to such rapid network reorganization. Together, our findings demonstrate that CA1 and PPC both update their representations over experience, but with distinct population-level signatures, suggesting that learning is supported by different modes of plasticity across the hippocampus and neocortex.

Disclosures: Z. Khan: None. **I. Voitov:** None. **A. Shah:** None. **A. Losonczy:** None. **S. Fusi:** None.

Poster

PSTR078: Cortical Circuits and Navigation

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Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.12/LL3

Topic: I.09. Spatial Navigation

Support: Whitehall Foundation Research Grant

Title: Bottom-up vs. top-down influences on egocentric goal coding

Authors: *M. RASHED-AL-MAHFUZ[1], J. R. HINMAN[2];
[1]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Dept. of Psychology, Univ. of Illinois Urbana-Champaign, Champaign, IL

Abstract: Goal-directed navigation requires animals to translate goal locations into egocentric action plans relative to their own body axis. These goals can be specified by bottom-up sensory cues or by top-down mnemonic signals, yet whether egocentric goal representations are constructed from sensory or memory information, and where in the brain this occurs, remains unresolved. Using head-mounted miniscope calcium imaging in mice, we previously identified Convergent Sink (ConSink) cells in the dorsomedial striatum (DMS) whose egocentric bearing tuning converges on the reward location and dynamically remaps as the reward moves, establishing that DMS encodes goal bearing in an egocentric frame. However, because reward was delivered at a physical dish, this design could not dissociate egocentric coding of the remembered goal from coding of the salient sensory object marking it. To resolve this, and to ask whether such coding is built from top-down or bottom-up inputs, we developed an automated octagonal arena (110 cm across flats) with a 145-well Cheeseboard floor; any well can be baited with sucrose water from beneath via an automated pump, so reward can appear at a location with no external cue. Eight LED nosepoke ports line the perimeter walls, and an overhead laser array can mark any floor well with a visible cue, letting an identical goal be made either memory- or sensory-defined. In a first task, rats alternate within a session between navigating to a single unmarked, learned reward well, whose location changes several times per session, and to sensory-cued perimeter ports, directly contrasting memory- and sensory-guided egocentric coding. Electrophysiological recordings of DMS neurons corroborated the previous calcium imaging results and allowed for the dissociation of the influence of memory and sensory influences. In a second task, a continuous-trial variant of the classic Cheeseboard maze, rats start

each trial from one of eight perimeter locations rather than a start box and learn a new three-well reward sequence each day; running the same sequence under laser cuing yields a sensory-guided session matched to the memory condition in reward structure, motor demands, and trial sequence. Rats readily learned this challenging task structure, which will allow investigation of whether retrosplenial cortex (RSC), positioned to integrate top-down hippocampal mnemonic input with bottom-up posterior parietal sensory input, encodes egocentric goal direction differentially across memory- and sensory-guided navigation, revealing how egocentric goal representations are constructed and transformed across reference frames.

Disclosures: M. Rashed-Al-Mahfuz: None. **J.R. Hinman:** None.

Poster

PSTR078: Cortical Circuits and Navigation

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Program #/Poster #: PSTR078.13/LL4

Topic: I.09. Spatial Navigation

Support: Whitehall Foundation Research Grant

Title: Representations of conspecifics in the anterior cingulate cortex, posterior parietal cortex and retrosplenial cortex of freely behaving rats

Authors: *R. M. BURCH[1], Y. DAI[2], M. RASHED-AL-MAHFUZ[4], A. RADEV[5,2], V. KOSTOV[6], J. R. HINMAN[3];
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Abstract: The field of spatial navigation has elucidated neural representations that encode stable environmental features such as boundaries, environmental geometry, landmarks and locations. However, naturalistic environments contain dynamic stimuli, including conspecifics. Animals must navigate physical and complex social environments in which conspecific's locations change. Tracking conspecifics is critical for context appropriate social behaviors that guide vital decisions within groups. Conspecific coding has been observed; CA1 neurons represent locations of conspecifics while simultaneously encoding information of conspecific's identity across multiple species. Higher-order cortical areas, such as the anterior cingulate cortex (ACC), posterior parietal cortex (PPC), and retrosplenial cortex (RSC) integrate relevant sensory experiences guiding social behavior. These regions are theorized to support the transformations between allocentric and egocentric spatial references frames, a process necessary for spatial navigation. Although these regions are implicated in both social processing and spatial cognition, little is known about their contributes to egocentric spatial representations of conspecifics. To determine the roles of ACC, PPC and RSC in egocentric spatial processing of conspecifics, we

conducted in vivo electrophysiological recordings using silicon probes in freely behaving male Long Evans rats. Neural activity was recorded during interactions with familiar and novel conspecific as well as familiar and novel objects presented within a wire mesh cylinder during separate 15 minute sessions. This design enables comparisons between social and non-social stimuli, allowing us to distinguish neural activity associated with the location of environmental stimuli from activity associated with conspecifics, while the inclusion of novel and familiar stimuli allows us to evaluate if this neural activity is driven by sensory experiences or is additionally influenced by previous experiences. We hypothesize that the ACC, PPC and RSC contribute to egocentric representations of social environments, encoding socially relevant spatial information, including the location of conspecifics. Analyses identified neurons in the ACC, RSC and PPC whose activity encodes egocentric spatial information of conspecific location. Additionally, RSC and PPC neurons provide additional egocentric representations of environmental features, such as boundaries. This evidence suggests that higher-order cortical networks provide socially relevant spatial information that supports navigation and social behaviors in dynamic environments.

Disclosures: R.M. Burch: None. **Y. Dai:** None. **M. Rashed-Al-Mahfuz:** None. **A. Radev:** None. **V. Kostov:** None. **J.R. Hinman:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.14/LL5

Topic: I.09. Spatial Navigation

Support: NIMH R56 MH133929
R01 AG070094
Florida DOH 20A09
NIA F31AG079619-01

Title: 40Hz hippocampal stimulation as a restorative treatment for sleep and spatial navigation in Alzheimer's Disease

Authors: *E. M. SALVADOR[1], S. D. CUSHING[2], T. M. RAGSDALE[1], C. A. DAVIS[1], S. C. MOSELEY[1], A. C. STIMMELL[1], A. A. WILBER[1];
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Abstract: Memory replay during sleep involves functional interactions across the hippocampal-cortical network that are critical for learning-related plasticity (Ego-Stengel & Wilson, 2009; Jadhav et al., 2012; Maingret et al., 2016). We previously found deficits in coordination across the hippocampus (HPC) and parietal cortex (PC) during sleep in a young mouse model (3xTg-AD) of Alzheimer’s Disease (AD), which coincided with spatial learning and memory

impairments (Cushing et al., 2020). Recent research has shown effective clearance of AD pathology in mice (Iaccarino et al., 2016; Martorell et al., 2019) and improved functional connectivity in preclinical AD patients (He et al., 2021; Paulson et al., 2024) using 40Hz stimulation. We used optogenetic 40Hz entrainment targeting the hippocampus to assess the impacts on HPC-PC coordination and subsequent behavioral performance in 3xTg-AD/PV^{cre} mice compared to age-matched control and 3xTg-AD mice that received no stimulation. We implanted a 16-tetrode recording array target PC and HPC, and an optical fiber targeting HPC. Recording sessions of rest-task-rest took place daily, followed by HPC optogenetic stimulation using 40Hz entrainment or sham. We assessed sleep quality metrics, PC delta waves (DW), and HPC markers of memory replay (SWRs) during slow wave sleep. We also assessed intracellular density of phosphorylated tau (pTau) and two conformation specific antibodies preferring A42. 40Hz stimulation ipsilateral or contralateral to cellular recordings appeared to rescue spatial learning and temporal coordination of SWR-DW compared to sham stimulated mice. However, this measure of HPC-PC interaction no longer predicted behavior as in healthy control animals. Alternatively, 40Hz stimulation did restore hippocampal cross-frequency coupling of the theta and gamma bands, which subsequently predicted behavior performance as in controls. Both 40Hz and sham stimulation reduced beta amyloid load, though only 40Hz was capable of further reducing A42 in PC. 40Hz stimulation of HPC thus rescued learning and memory related functional interactions across the HPC-PC network during sleep, and impairments in spatial navigation. Observed effects seem to be mediated by direct 40Hz impacts on brain activity patterns.

Disclosures: E.M. Salvador: None. **S.D. Cushing:** None. **T.M. Ragsdale:** None. **C.A. Davis:** None. **S.C. Moseley:** None. **A.C. Stimmell:** None. **A.A. Wilber:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.15/LL6

Topic: I.09. Spatial Navigation

Title: Unraveling egocentric and allocentric to egocentric transformation impairments in TgF344-AD rats using a novel Map to Action Transformation Task.

Authors: *E. C. ELLIS[1], A. BREA GUERRERO[3], E. SALVADOR[2], A. A. WILBER[4]; [2]Psychology, [1]Florida State Univ., Tallahassee, FL; [3]Psychology, Florida State Univ. Program In Neurosci., Tallahassee, FL; [4]Psychology, Florida State Univ. - Program in Neurosci., Tallahassee, FL

Abstract: Understanding the early cognitive impairments associated with Alzheimer's Disease (AD) requires innovative approaches, including those that go beyond traditional behavioral assessment. Naturalistic navigation requires the use of different spatial reference frames, including allocentric (world-centered) and egocentric (self-centered). Impairments in the ability

to integrate and contextualize these reference frames are observed in neurodegenerative diseases like AD, both in humans and non-human animal models. Despite this, most rodent navigation studies in the AD field use tasks that focus on allocentric navigation. Human studies have revealed that the transformation between reference frames may be a key deficit in the navigation impairments observed in humans with and at risk for developing AD. To test this hypothesis, we developed and employed a novel behavioral test, the Map to Action Transformation Task (MATT), designed to dissect navigational processes for allocentric and egocentric reference frames and the transformation between them. We assessed MATT performance in a longitudinal study with assessments at 3- 6- and 9- months in TgF344-AD rats and littermate controls. Preliminary MATT data revealed egocentric deficits develop between 3 and 6-months of age in TgF344-AD rats, with transformation impairments emerging between 6 and 9-months. Allocentric impairments were not observed at any age. MATT's sensitivity and discriminative capacity allowed us to identify egocentric and transformation deficits in AD development that are distinct from one another, and from the allocentric deficit. Prior longitudinal work identified that TgF344-AD rats develop an allocentric deficit at a later time point, consistent with our findings on the allocentric condition of the MATT. These findings suggest that the navigation challenges seen in animal models for AD could be attributed to a combination of factors rather than solely to deficits in a specific reference frame. This emphasizes that navigation involves integrating different spatial perspectives, which may be impaired in AD due to a system-wide dysfunction rather than region-specific pathophysiology.

Disclosures: E.C. Ellis: None. **A. Brea Guerrero:** None. **E. Salvador:** None. **A.A. Wilber:** None.

Poster

PSTR078: Cortical Circuits and Navigation

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR078.16/LL7

Topic: I.09. Spatial Navigation

Support: NINDS R00NS134734
NCI 1U54CA272205
University of Maryland School of Medicine
University of Maryland - Medicine Institute for Neuroscience Discovery

Title: Dynamics of nonlocal spatial coding in the entorhinal-hippocampal network over trials, days, and environments

Authors: *K. HUMMEL[1], G. BROWN[2], L. M. GIOCOMO[3], E. AERY JONES[4];
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Abstract: Spatial memory is an associative process that represents environmental stimuli through neural representations. These representations can be coded by neuronal firing in the medial entorhinal cortex (mEC) and hippocampus , both during active exploration and during periods of immobility. Recently, studies have found that during immobility, neurons in the mEC can represent spatial positions distal from the animal's current location in an environment, a phenomenon called nonlocal coding. Here, we characterize the temporal and spatial dynamics of these nonlocal representations. We recorded simultaneously from mEC, CA1, and CA3 *in vivo* while mice performed a spatial alternation task and freely foraged. First, nonlocal coding emerged rapidly over the course of an initial exposure to a novel environment and was stably present across multiple days. Ongoing work will examine how different levels of cognitive demand across different environments alter nonlocal coding. Second, we tracked individual cells and found that the same cells are preferentially recruited to immobile nonlocal coding over trials. Ongoing work will continue this analysis by tracking cells over days and environments. Third, we found high rates of immobile nonlocal coding in CA1, but of different locations than those represented by mEC. Ongoing work with higher density recordings to achieve better decoding accuracy will reveal the flow of information along the superficial mEC to CA3 and CA1 circuit during immobility. Fourth, prior work has shown that nonlocal coding can be pertinent behavior, representing task-relevant locations at appropriate times. Ongoing work will dissect the relationship between nonlocal coding and salient landmarks, to determine if reward or strong salience is required for representation during immobility. In sum, this data will uncover how remote representations of spatial information form, evolve, and adapt to novel environments, and give us a stronger understanding of spatial memory formation.

Disclosures: K. Hummel: None. **G. Brown:** None. **E. Aery Jones:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.01/LL8

Topic: I.11. Language

Support: JST Moonshot R&D Grant Number JPMJMS2011

Title: Cortical Speech Decoding Favors Syllable-Scale Representations in Predominant CV-Structured Language

Authors: *Y. LIU[1], M. HIRATA[2,1];
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Abstract: State-of-the-art speech brain-computer interfaces (BCIs) in English adopt phonemes as decoding units, reflecting the phonological structure of English, which has a large inventory of syllables (~15,000) but a small phoneme set (44 phonemes). In contrast, studies in Japanese and

Mandarin often use syllable-scaled units for speech decoding, motivated by their predominantly CV (consonant-vowel) structure, and the ratio of syllable-scaled units to phonemes is less than 10:1. This divergence raises a fundamental question: is the optimal neural decoding unit universal, or determined by a language's phonological organization? To reveal this under the matched linguistic conditions, we first built a corpus containing 42 morae and 20 phonemes, whose unit distributions can reflect the natural Japanese usage. Then we recorded stereo-EEG from 8 native Japanese speakers during speech production and compared phoneme and mora-based (syllable-scaled unit) decoding under matched conditions. High-gamma activity was widespread across the cerebral cortex, but only a small minority of electrodes tracked articulatory kinematics, indicating that most decodable signals arose from cerebral sites engaged in speech processing rather than motor-articulatory patterns. At the single-electrode level, mora-based decoding showed higher accuracy and lower temporal variability in both linear and non-linear machine learning models, despite largely overlapping informative sites. To test whether this advantage persisted beyond articulatory-related sites, we removed electrodes with significant articulatory tuning identified by STRF analysis and trained a customized deep network (8-layer CNN + bidirectional LSTM + CTC loss) for the rest of the electrodes. Again, mora-based decoding showed a higher whole-word (highest 98.6%) and syllable-scaled unit-level accuracy. All participants showed at least 7% improvement in the whole word level accuracy, whereas character error rates did not differ statistically between mora and phoneme models. These findings not only demonstrate that syllable-scaled units provide more stable neural representations than phonemes in predominant CV-structured languages but also indicate that accurate speech decoding can be achieved from cortical regions outside articulatory control. Thus, the optimal neural speech decoding unit is not universal, and the choice of neural decoding unit should depend on a language's phonological structure, informing cross-linguistic BCI design and electrode-placement strategies.

Disclosures: Y. Liu: None. **M. Hirata:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.02/LL9

Topic: I.11. Language

Title: Semantic prediction errors localize to bilateral superior temporal gyrus, dissociable from acoustic and phonotactic surprise

Authors: *A. ZADBOOD, G. HORGA;
Columbia Univ., New York, NY

Abstract: Predictive processing theories propose that the brain continuously generates expectations about incoming input, with prediction errors (PE) driving cortical computation. How and where semantic predictions are encoded during natural language remains unclear: most

LLM-derived PE measures use word-level cross-entropy, conflating semantic with syntactic surprise. We developed a framework that isolates a predominantly semantic PE signal in continuous speech and maps it across a nested feature hierarchy. We built a ROCStories selectivity benchmark using 1,000 stories paired with meaning- and form-altered endings, evaluating 41 LLMs for sensitivity to meaning over form. Qwen3-Embedding-8B led the benchmark and was used to compute a semantic PE regressor: cosine dissimilarity between the current and next phrase each embedded together with a few sentence narrative summary. Per-subject nested ridge encoding models were fit to a 24-parcel dual-stream language atlas in two continuous-narrative fMRI datasets (Pieman N=73, Not The Fall N=54) and, as a stimulus-structure control, in healthy listeners hearing disjoint sentence blocks (N=25) where multi-sentence context cannot accumulate.In continuous narrative, semantic PE produced the largest beta magnitudes of any PE feature, localizing to bilateral STG, with the most reliable effects in the left posterior STG and replicating across datasets (L pSTG: Pieman t(72)=7.63, p=7.5e-11; Not The Fall t(53)=6.61, p=1.9e-8; bilaterally significant in anterior and posterior STG). In the sentence-block control, the same regressor produced no reliable signal (L pSTG beta 0.77 to -0.06; 0/24 FDR-sig), confirming that the STG response indexes accumulated narrative prediction, not sentence-local surprise. Low-level features localized instead to bilateral primary auditory cortex across all three datasets: phonotactic surprisal and acoustic envelope peaked in Heschl's gyrus and planum temporale. This reveals a posterior-to-anterior gradient along the superior temporal lobe, from form-level surprise in primary auditory cortex to context-dependent meaning-level prediction in lateral STG.These results identify a cortical substrate for meaning-level prediction in the bilateral STG, dissociable from lower-level acoustic and linguistic surprise and dependent on multi-sentence context.

Disclosures: A. Zadbood: None. **G. Horga:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.03/LL10

Topic: I.11. Language

Support: NIH Grant NINDS 1R01NS109367
NIH Grant NINDS 1R01NS115929
NIH Grant NIDCD R01DC018805

Title: Human cortical representation of imaginary speech

Authors: *L. YU[1], Y. HUANG[3], P. C. DUGAN[4], W. K. DOYLE[5], A. MICHALAK[6], P. A. ROZMAN[2], D. FRIEDMAN[4], A. FLINKER[7];
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Abstract: The majority of us have internal dialogues, but the cortical networks that support imagined speech are not well understood. While it is well established that the Inferior Frontal Gyrus (IFG) and Precentral Gyrus (PrCG) play critical roles in overt speech, it is not clear how temporal dynamics and representation adapt when speech is imagined. We aim to identify cortical network that supports imagined speech and establish forms of pre-articulatory representation in IFG regardless speech is imagined or overt in nature. We obtained electrocorticography (ECoG) data when patients (N = 31 patients, 1024 active electrodes) were performing a series of speech production tasks requiring either imagined or overt speech responses, including picture naming, visual reading, auditory repetition, auditory naming, and sentence completion. All tasks used the same set of 50 words randomly interspersed within block, but with different retrieval routes. Paired t-tests were conducted to determine the co-activation and statistical significance of difference in neural activity (high gamma broadband, 70-150 Hz) locked to articulation (the onset of articulation in imagined condition was estimated with RT in overt condition and cross-correlated with sensory responses). We find that electrodes within the IFG show similar activation 250 ms prior to articulation during imagined speech regardless of motor output. In contrast, the PrCG activity peaks prior to speech onset in imagined condition, whereas in overt speech, it continues to increase and peaks shortly after articulation onset. Applying multivariate temporal response functions and variance partitioning revealed that the IFG maintains shared acoustic representations across conditions. Notably, articulatory kinematic features remained significantly encoded during imagined speech despite absent motor execution. Spatially, this encoding clustered at the IFG-middle frontal gyrus junction, mid-dorsal PrCG, and anterior superior temporal gyrus. These findings establish the distinct spatiotemporal roles of the IFG and PrCG, highlighting the potential of non-motor speech neuroprostheses.

Disclosures: L. Yu: None. **P.C. Dugan:** None. **W.K. Doyle:** None. **A. Michalak:** None. **P.A. Rozman:** None. **D. Friedman:** None. **A. Flinker:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.04/LL11

Topic: I.11. Language

Support: UMass Institute for Diversity Sciences

Title: Visual Speech Facilitates Acoustic, Lexical, and Syntactic Speech Processing

Authors: *Y. WANG, L. SANDERS;
Univ. of Massachusetts Amherst, Amherst, MA

Abstract: Models of how people grasp meaning from speech signals require high-level linguistic processing in addition to low-level acoustic representations. Mapping multiple levels of language representations onto listeners' scalp electroencephalogram (EEG) has provided important

information about how the human brain encodes and decodes auditory-only speech. However, the type of face-to-face communication that is typical of conversations throughout human evolutionary history includes visual and auditory speech signals. Effects of visual speech on auditory processing and, especially under challenging listening conditions, benefits to comprehension are well documented. However, the connection between visual speech reducing neural responses to auditory speech and supporting comprehension remains elusive. To investigate the contributions of visual information to multiple levels of speech processing, we recorded EEG and manipulated selective attention and the presence of distractors while participants listened to stories for comprehension. Specifically, a female talker was presented as audiovisual or audio-only, with or without a concurrent audio-only male talker, when listeners were instructed to attend to the female talker or to the male talker. Temporal response functions (TRFs) were calculated to characterize neural tracking of the low-level acoustic features captured by the speech envelope and high-level linguistic features, including word onsets, lexical and syntactic surprisal, and syntactic node count. The added predictive benefits of the included high-level linguistic features were significantly greater for audiovisual than for auditory-only speech. TRF morphology further showed reduced early responses to the acoustic envelope in audiovisual versus auditory-only speech, but enhanced later responses to lexical and syntactic features, especially under adverse listening conditions. These findings indicate that visual speech modulates language processing in different ways at different stages; visual speech decreases processing demands of early auditory detection and processing while promoting greater engagement in predictive coding of high-level semantic and syntactic features at later stages of processing. Together, these findings extend previous work based on auditory-only speech and advance the understanding of the multiple ways in which visual speech is a critical and typical part of successful speech communication.

Disclosures: Y. Wang: None. **L. Sanders:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.05/LL12

Topic: I.11. Language

Title: In silico model of the human speech cortex generalizes across individuals and real-world contexts

Authors: *S. JAIN[1], C. CHO[3], M. SATO[2], S. HU[2], S. KUNNAM[2], A. IYER[1], J. GAUTHIER[2], R. GANDHI[2], G. K. ANUMANCHIPALLI[4], E. F. CHANG[5];
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Abstract: A central goal of neuroscience is to uncover the organizing principles that govern human brain function across individuals and contexts. Yet most computational models of the human brain remain narrowly trained on single datasets, limiting their ability to generalize across people, tasks, and experimental conditions. Here, we introduce the first digital simulation of the human cortex that can mimic brain function across hundreds of individuals and diverse real-world scenarios. Focusing on speech perception and intracranial recordings, we develop a large-scale neural network that can synthesise diverse neural responses to learn the intrinsic functional organization of human speech cortex. Through this, it can bidirectionally map speech stimuli and neural activity in a zero-shot manner, without subject-specific training. As a neural encoder, the digital simulation accurately predicts the neural spectrum, phase and LFP in new individuals and experimental paradigms. Going beyond prediction performance, we also show that it corroborates several established findings, acting like an in silico model of the human speech cortex. As a speech decoder, the digital simulation accurately predicts speech from a new individual's brain activity, operating as an out-of-the-box brain-computer-interface (BCI). We also show that it transfers zero-shot to participants in a speech BCI clinical trial. The digital simulation's performance improves systematically with increasing diversity of training data—across participants, tasks, stimuli, and electrode locations— enabling progressively richer representations of cortical function and stronger generalization to unseen conditions. By quantifying how predictive accuracy scales with dataset size and heterogeneity, we establish empirical neural scaling laws for the human speech cortex, providing a foundation for large-scale, data-driven models of brain function. Finally, we probe the digital simulation to develop a comprehensive map of the spatial organization of the human speech cortex.

Disclosures: S. Jain: None. **C. Cho:** None. **M. Sato:** None. **S. Hu:** None. **S. Kunnam:** None. **A. Iyer:** None. **J. Gauthier:** None. **R. Gandhi:** None. **G.K. Anumanchipalli:** None. **E.F. Chang:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.06/LL13

Topic: I.11. Language

Support: NSF Grant 2319491

Title: Pupil-linked brain states shape stimulus encoding and behavior during word learning

Authors: *D. LEE[1], A. QIN[1], E. F. CHANG[3], M. K. LEONARD[2];
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Abstract: During challenging tasks like learning a non-native language, moment-to-moment changes in broad physiological states can influence performance and learning outcomes.

However, the links between endogenous brain states, cortical processing of task-relevant information, and behavior remain unclear. Here, we examine these links by recording high-density electrocorticography (ECoG) with simultaneous pupillometry while English-speaking neurosurgical participants learn words in an unfamiliar language. In this challenging task, participants heard unfamiliar words and learned to produce their spoken English translations through trial-by-trial real-time feedback. We asked how pupil dilation during pre-stimulus rest, sound encoding, target retrieval, target production, and feedback relates to cortical activity during each of these task phases, and to what extent this relationship depends on the difficulty of discriminating the stimuli.
We found that pre-stimulus pupil diameter is negatively correlated with stimulus-evoked neural activity in cortical speech areas including the superior temporal gyrus (STG). This relationship was not uniform across all stimuli, but was stronger when the unfamiliar novel words were perceptually confusable compared to when the words were easier to discriminate. Furthermore, correlations between pupil and task-evoked activity during retrieval, production, and feedback indicate that pupil-linked physiological states influence neural responses at multiple sensory, perceptual, motor, and cognitive levels.
Together, these results suggest that endogenous physiological states, as indexed by pre-trial pupil dilation, are associated with fluctuations in how various perceptual and cognitive processes unfold in real-time. Selective regulation dependent on demand or difficulty further indicates that behavioral outcomes are not solely driven by task constraints, but rather are modulated by task-independent ongoing changes in broad physiological states like arousal. These findings offer a novel avenue for understanding how internal states shape the cortical basis of learning.
D.L. and A.Q. contributed equally.

Disclosures: D. Lee: None. **A. Qin:** None. **E.F. Chang:** None. **M.K. Leonard:** None.

Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.07/LL14

Topic: I.11. Language

Support: University of Rochester OP211716

Title: Localizing auditory semantic comprehension and associated ERP components: A stereo electroencephalography study

Authors: *K. K. TOFFOLO[1], M. E. TIVARUS[2], F. GARCEA[3], E. G. FREEDMAN[4], J. J. FOXE[5];
[1]Del Monte Inst. for Neuroscience, Univ. of Rochester, Rochester, NY; [2]Imaging Sci. and Neurosci., [4]Del Monte Inst. for Neurosci., [5]Neurosci., [3]Univ. of Rochester, Rochester, NY

Abstract: Comprehending meaning from spoken language is complex, operating across multiple scales (words, sentences, pragmatic discourse) and influenced by context, predictability, and sensory modality (reading vs. listening). Prior research has primarily suggested that language networks reflect either a fronto-temporal-parietal network model, or a “hub-and-spoke” model for which modality-specific brain regions communicate through a transmodal hub in the anterior temporal lobe (ATL). Additionally, the neural generators for the semantic N400 and P600 ERPs have largely been unresolved, particularly in response to auditory sentences. Given these gaps and the key role that auditory sentence processing plays in communication, this study utilized the precision of sEEG to characterize the neural activity underlying auditory semantic comprehension. The contribution of these auditory semantic data are critical to understanding the organization of our complex language network and could provide insight into potential physiological origins for the N400 and P600 components. Responses to sentences with/without semantic errors (ex. “I baked a birthday cake/clue) were recorded from 1,986 electrode contacts (1,026 right hemisphere; 960 left) across the brains of eighteen adult participants with intractable epilepsy. Significant semantic congruency effects were found at 153 contacts (75 right; 78 left), predominantly in bilateral ATL, the amygdala-hippocampal border, IFG, insula, and left posterior temporal areas, often with earlier latencies from more anterior contacts. Interestingly, significant activity from the left hemisphere was broadly distributed while the activity from the right hemisphere was more focal and “hub-like”. N400-like responses were primarily observed within the ATL (aSTG, planum polare, lateral temporal pole) and left anteromedial temporal structures (medial temporal pole), indicating that these regions likely contain neural generators for the N400 during auditory sentence comprehension. However, significant activity from several brain regions overlapped with the N400 and/or P600 time windows, suggesting that these scalp-recorded ERPs are the result of coordinated cognitive processes from a distributed network rather than being generated solely from one structure. Overall, these data suggest that auditory semantic comprehension does not follow a leftward dominant language pathway. Rather, activity was evoked from bilateral brain regions, especially within the ATL, with a processing network that was widely distributed within the left hemisphere and more localized and focal in the right hemisphere.

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Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

Time: Sunday, November 15, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR079.08/LL15

Topic: I.11. Language

Support: NIH K12 Neurosurgeons Research Career Development Program (PI: Grannan)

Title: Hippocampal-neocortical interactions mediate linguistic prediction and inference

Authors: *M. GHOSH[1], M. MAHON[3], S. LOWE-HINES[2], A. CRANDALL[4], Q. CHENG[3], P. BI[3], A. KO[5], J. A. HERRON[6], K. E. WEAVER[7], J. G. OJEMANN[8], B. L. GRANNAN[9]; [2]Neurosurg., [1]Univ. of Washington, Seattle, Seattle, WA; [3]Univ. of Washington, Seattle, WA; [4]Sch. of Med., Univ. of Washington, Dalton Gardens, ID; [5]Neurolog. Surgery, [6]Dept. of Neurolog. Surgery, [7]Radiology, [8]Dept Neurosurg., Univ. of Washington, Seattle, WA; [9]Neurolog. Surgery, Univ. of Washington Sch. Of Med., Seattle, WA

Abstract: When confronted with a novel input, the human brain has a remarkable ability to rapidly infer the probable meaning of the stimulus. Such inference can often be achieved after only a single stimulus exposure, a capacity referred to as zero-shot learning. Rapid inference is thought to be mediated by predictions, a topic of increasing interest in the fields of both neuroscience and artificial intelligence. Here we use intracranial, human brain recordings to uncover the neural mechanisms enabling linguistic prediction and inference in the human brain. Predictive processing in the brain has been found in several brain regions and input modalities. Evidence of predictive processing has also been found in language, mostly using EEG and fMRI studies. While most of the regions shown to be involved in linguistic predictions show high levels of functional specificity towards language, the hippocampus (HPC) in linguistic predictions stands out. Traditionally thought to play a key role in memory, navigation and contextual learning across species, there is growing evidence of the role of HPC in language and in predictive processing across several functions. The study of the hippocampus in prediction, language and contextual learning however has been undertaken in separate studies and hence its role during tasks combining these processes remains unknown. It has also been studied in isolation from other language regions and without the same electrophysiological detail that rodent HPC studies provide. Here we undertake a systematic investigation of hippocampal-neocortical activity using intracranial depth electrodes during linguistic contextual predictive processing leading to inference. We look at predictability on a finer scale during highly constrained sentences. We investigate the role of neural activity in each of these regions and their mutual interactions during the predictive and inference process across 20 subjects. Our results show robust encoding of predictability and inference that together suggest a hippocampal-neocortical role mediating these processes.

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Poster

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Title: Slow Traveling Waves as a Mechanism for Speech-Induced Suppression in Human Auditory Cortex

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Abstract: During speech production, the brain distinguishes self-generated from externally-produced speech through speech-induced suppression. This suppression arises from transmitting a blueprint of the motor signal to sensory cortices prior to vocalization, referred to as a corollary discharge. However, the neural mechanisms by which auditory cortex receives this information and is suppressed remain poorly understood. We hypothesized that traveling waves in the auditory cortex may coordinate neural suppression across the superior temporal gyrus (STG) in advance of speech onset. Using high-density Electrocorticography (ECoG) recordings from STG during multiple production tasks (Auditory Repetition, Picture naming, and Visual Word Reading), we tested this hypothesis by asking if pre-speech traveling waves are correlated with the degree of auditory suppression at individual electrodes' high-gamma (70-150 Hz) activity. We computed the instantaneous phase at a low-frequency (2-5 Hz) band and derived spatial phase gradients across local electrode neighborhoods. We then quantified traveling wave activity using Phase Gradient Directionality (PGD, Rubino et al., 2006), which quantifies how consistently phase-gradient vectors align across the neighborhood. Focusing on a window spanning 500 ms before to 300 ms after speech onset, we found that in a subset of STG electrodes, PGD was robustly elevated, indicating the presence of traveling waves. Critically, across all tasks, the trial-averaged PGD within this window was strongly correlated with each electrode's high-gamma Suppression Index ($r = 0.789$, $N = 54$, p-value$<$1e-5): electrodes exhibiting stronger traveling wave activity showed greater suppression of auditory responses during self-generated speech. To confirm that this traveling wave activity reflects a reliable, recurring neural phenomenon rather than an artifact of trial averaging, we further examined the Inter-Trial Coherence (ITC) of the phase gradient direction across trials. Electrodes with high PGD also showed significantly elevated ITC, demonstrating that the direction of phase propagation was consistent across trials, traveling along the superior-to-inferior cortical axis. These findings suggest that low-frequency traveling waves in STG may serve as a preparatory mechanism associated with the suppression of auditory responses during self-generated speech.

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Title: Intracranial Recordings Reveal Temporo-Parietal Junction as the Earliest Site Sensitive to Linguistic Constituency Structure that Dissociates from Visual Geometric Recursion

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Abstract: How the human brain builds meaning from basic phrases remains mostly unknown. Models differ on the exact contributions to this process from frontal, temporal and parietal cortices. We performed an intracranial investigation of phrase reading using subdural grid electrodes or stereotactically placed depth electrodes (sEEG) in 25 participants. We implemented a 'Minimal Structure' paradigm of 3-word phrases presented in RSVP (500ms per word) involving Function/Content manipulations, with violations created by intentionally misplaced/nonsense function words. Content words contained a mix of categories. Phrases with Function-Function pairs were used to trigger syntactic inferences without strong semantic demands. Combinations of these words preceded a third phrase-completing word. Participants made acceptability judgments. Behavioral performance was high (>90%) and only correct trials were analyzed. We contrasted grammatical trials ('to the car', 'the fast car', 'drive the car', 'drive quickly now') with agrammatical ('they the car') and asemantic ('ti the car') trials. We analyzed structure-sensitive electrodes in high gamma power (70-150Hz). For grammatical vs. ungrammatical Function-Function trials, a region in temporoparietal junction (TPJ) showed greater activity for violations as early as second word presentation, while posterior IFG showed a decrease but only during third word presentation. To more conservatively isolate phrase structure effects, we contrasted all acceptable vs unacceptable phrase types (regardless of lexical category). The only region to survive this contrast was a narrower strip of the previously mentioned TPJ - portions of the most posterior extent of pSTS bordering parietal cortex - aligning with recent lesion-symptom mapping research that has "pushed back" the core causally-derived syntax site from previously-believed MTG. This suggests that this posterior syntax hub generates structural properties of phrases, while in parallel pIFG engages in integration, repair, or lexical-semantic control. In three patients, we used a separate paradigm to isolate visual recursive processing using a series of increasingly complex geometric shapes that either violated or adhered to a recursive rule. We discovered that all of the cortical sites sensitive to visual recursion in TPJ were immediately neighboring but distinct from linguistic sites, but in frontal cortex there was partial overlap, suggesting that the pSTS-TPJ syntax hub contains cortical patches more focally dedicated to linguistic structure vs. domain-general control.

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Poster

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Title: Polysemanticity in human hippocampal neurons

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Abstract: *To comprehend language, the brain must navigate a high-dimensional semantic landscapewhile seamlessly contextualizing meaning. Inspired by recent advances in the mechanisticinterpretability of large language models (LLMs), we hypothesized that the brain utilizespolysemanticity, a coding strategy wherein individual neurons represent multiple semanticallyunrelated features through high-dimensional superposition (Elhage et al., 2022; Olah et al.,2020). We recorded single-unit activity from the human hippocampus during podcast listening.We found that hippocampal neurons exhibit dense semantic codes characterized by multipletuning peaks with an overdispersed, isotropic geometry. This geometry satisfies the theoreticalrequirements for interference minimization in superimposed codes. Furthermore, semanticresponses are strongly modulated by lexical and speaker-identity context; nonetheless, theunderlying population geometry remains stable. This coding strategy permits rapidcontextualization without requiring specialized, context-specific neurons. Indeed, we show clearpattern separation of similar terms, along with pattern completion for held-out words. Together,these results demonstrate that the human brain leverages superposition to solve a universalcomputational problem: maximizing semantic capacity within a constrained representationalspace.*

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Poster

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Support: NIH NIDCD R01 DC020717

Title: iEEG activity in the STG encodes features from silent visual speech during natural sentences

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Abstract: Visual speech information, such as visemes, improves auditory speech perception, particularly in noisy listening environments. Despite strong behavioral evidence, the neural mechanisms by which visual information facilitates auditory processing remain poorly understood. Prior work from our lab and other groups has demonstrated that visual speech can modulate auditory neural representations of phonetic and potentially phonemic information. However, most existing research has primarily relied on artificial arrangements of isolated phonemes or single-word stimuli that fail to capture the full distribution of phonemes present in everyday speech, limiting our understanding of audiovisual speech perception in ecologically valid contexts. To address this gap, we developed an intracranial electroencephalography (iEEG) task consisting of 100 phonetically balanced sentences: 50 presented in the auditory-alone condition and 50 presented in the visual-alone (i.e., silent) condition. Stimuli were selected from the TCD-TIMIT corpus, a phonetically rich audiovisual dataset, and averaged approximately 33 phonemes and 8.5 words per sentence. Six epilepsy patients completed this task, identifying the target word at the end of each sentence for both conditions. Preliminary analyses focused on one patient with multiple electrodes in auditory and audiovisual speech regions, including Heschl's gyrus, the posterior superior temporal sulcus, and the superior temporal gyrus (STG). Using both encoding and decoding models, we tested whether phonetic features were represented at electrodes in the auditory system in both auditory-alone and visual-alone sentence perception.

Consistent with prior findings, phonetic features were encoded in the STG both for the auditory modality and, to a weaker degree, the visual modality. Specifically, consonants were better encoded than vowels in the visual-alone condition. Our results align with prior findings that phonetic information can be classified in auditory regions from visual speech in well-controlled tasks using phonemes and single words. Together, these data further support a model of audiovisual processing in which visemes enhance population-tuned auditory representations, facilitating speech comprehension under challenging listening conditions.

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Poster

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Title: Toward stimulation-free intraoperative language mapping: clinical, cross-linguistic and electrophysiological validation of an intraoperative language test.

Authors: *G. DE OLIVEIRA SANTOS SOUZA[1], P. S. CAMARGO[2], A. M. MORGAN[3], A. AREVALO[4], A. FLINKER[5], G. LEPSKI[1];
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Abstract: Direct electrical stimulation (DES) is the gold standard for intraoperative language mapping during awake craniotomy. However, it carries an increased risk of seizures, thus precluding its use in certain at-risk patients. Electrocorticography (ECoG) enables broader, passive monitoring of language processes at a lower seizure risk; still, its use as an alternative to DES requires one to ensure that intraoperative tasks reliably and specifically elicit high-gamma activity (70-150 Hz) for accurate mapping. Current mapping protocols are further limited by relying almost exclusively on naming paradigms, leaving many language-network functions unassessed. We developed the Mini-Intraoperative Language Test (MILT), a novel battery assessing 12 linguistic abilities, including verbal fluency, verb generation and auditory naming, among others, all applied during approximately three minutes of continuous monitoring. Pilot data from two patients undergoing awake craniotomy for brain tumor resection in Brazil (DES contraindicated due to epileptogenic history) confirmed the protocol's feasibility and sensitivity. The battery successfully detected task-specific deficits. In one patient verbal fluency deficits

were most evident, while picture naming remained intact, which directly influenced surgical resection. To establish the electrophysiological validity of the MILT tasks for ECoG-based mapping, the battery is currently being translated into English and implemented at New York University Langone Health in patients with refractory epilepsy undergoing invasive monitoring with stereo-electroencephalogram (sEEG). This controlled inpatient setting provides a unique opportunity to determine whether MILT tasks elicit reliable, task-specific high-gamma responses, which is necessary for eventual clinical implementation as a stimulation-free language mapping tool. High-gamma signals were extracted via Hilbert transform following common average referencing and analyzed per task domain. This multi-site, cross-linguistic design addresses clinical proof-of-concept and electrophysiological validation, contributing to a comprehensive, seizure-safe alternative to DES for intraoperative language network mapping.

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Poster

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Title: The influence of linguistic predictability on the encoding of speech in human auditory cortex: an intracranial EEG study

Authors: *W.-C. LIN[1], J. DOU[1], Z. LI[1], A. RUDAEVA[2], A. R. NIDIFFER[1], S. V. NORMAN-HAIGNERE[1], E. C. LALOR[1];
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Abstract: The idea that top-down, knowledge-based information influences the processing of bottom-up sensory signals has become central to contemporary accounts of perception. Speech perception, in particular, is increasingly understood as involving the integration of incoming sensory input with expectations derived from contextual information. Recent scalp EEG studies suggest that predictive feedback can influence early acoustic-phonetic encoding of speech, but the cortical organization and mechanisms underlying this effect remain unclear. Here, we addressed these questions using intracranial EEG (iEEG), which provides high spatiotemporal resolution for examining predictive influences across human auditory cortex. We analyzed iEEG recordings from 10 neurosurgical patients as they listened to ~24 minutes of naturalistic speech. We found that, across the majority of electrodes (120 of 134) in the auditory cortex, neural tracking of the speech envelope was stronger for more surprising words, consistent with enhanced encoding of prediction errors. Moreover, the correlation between neural tracking and lexical surprisal (hereafter termed the “prediction index”) increased with speech selectivity but

not anatomical distance from primary auditory cortex. Hierarchical linear mixed-effects modeling further provided Bayesian evidence that speech selectivity had a larger effect on the prediction index than anatomical distance. Slow speech was also found to have larger prediction indices than fast speech. Together, these findings support the notion of functionally organized, top-down feedback driven by context-based predictability.

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Poster

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Title: A neural code for generative speech production in human Wernicke's area

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Abstract: Wernicke's area, in the left superior temporal cortex, is regarded as a core region for understanding speech, yet damage to it profoundly impairs speech production. Why injury to a region for perceiving speech should disrupt the ability to produce it has remained unresolved. Using intracranial recordings of neuronal populations and single neurons, together with electrical stimulation and lesion analysis, we show that this territory is not functionally uniform: embedded within it is a discrete subregion of the left posterior superior temporal gyrus (lpSTG) that supports not only the perception of speech but also its production. Beyond responding during listening, the lpSTG becomes active before a person begins to speak, anticipating the words to come. Stimulating lpSTG causes speech arrest and sound errors, showing that it is directly required for production. During natural speech, lpSTG encodes upcoming words, distinct from the articulatory signals in motor cortex and the acoustic signals in neighbouring auditory populations. Furthermore, individual neurons in lpSTG are separable from nearby cells that track the sound of one's own voice. Finally, in a person with paralysis, activity in lpSTG is sufficient to decode both heard and intended speech. These findings reveal that Wernicke's area is not a single perceptual region but harbours a distinct production hub, where speech is assembled into words before it is spoken, resolving the long-standing puzzle of why damage there disrupts

speech production.
A.S. and M.K.L contributed equally.

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Poster

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Topic: I.11. Language

Title: Signal-processing Choices Determine Single-Unit Yield in Awake Human Neuropixels

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Abstract: Neuropixels are increasingly being deployed in the human intraoperative setting, demonstrating safety and feasibility of using these devices to record single neurons. Realizing this potential, however, remains substantially challenging. The shank is fragile, and the motion of the pulsating brain continuously shifts the positions and the waveforms of recorded neurons across recording channels over the course of a recording, and can even risk fracturing the device. The intraoperative environment is also saturated with electrical interference that degrades signal quality and, if not properly addressed, can entirely mask single-unit responses. Together, brain motion and electrical interference are the two principal factors limiting single-unit yield in human Neuropixels recordings (Chung et al., 2022). A growing set of offline tools (e.g., DREDge, IBL) and spike sorters are used to effectively mitigate these problems, but their parameters and relative performance have not been systematically evaluated on human intraoperative data - a gap that directly constrains yield and impacts all centers now adopting human Neuropixels.Here, in a large dataset of human Neuropixels recordings from 18 patients performing language tasks during awake DBS, tumor resection, or epilepsy surgery, with probes implanted in left and right posterior superior temporal gyrus (pSTG) and left posterior middle frontal gyrus (pMFG), we systematically quantify how core signal-processing choices shape single-unit yield, indexed by the number of task-responsive neurons recovered before and after key steps in the processing pipeline. We evaluate: (i) filtering, (ii) referencing and artifact removal, (iii) drift estimation and correction parameters, and (iv) choice of spike sorter testing these effects on our collected dataset, as well as synthetic and annotated data with ground truth. We show that human intraoperative data carry noise profiles and brain motion that challenge

current sorters and pipelines in non-trivial ways not captured by existing benchmarks. Building on these results, we identify processing configurations that substantially increase task-responsive yield beyond current pipelines - recovering, for example, 20 units responsive to a language-task-event in a patient where standard processing yielded only 3. This provides a practical validated framework to maximize yield as human Neuropixels recordings are adapted more broadly.

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Topic: I.11. Language

Title: Spatiotemporal dynamics of lexical access across task demands and networks

Authors: *J. QIAN[1], N. SHI[2], M. M. HAGLUND[6], B. FRAUSCHER[3], D. G. SOUTHWELL[4], G. B. COGAN[5];
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Abstract: Lexical access, the mapping of acoustic input onto stored word representations in the brain, is a foundational computation in language comprehension. The cortical network supporting lexical access and its rapid, competitive dynamics are increasingly well characterized, yet a central unresolved question is whether the resulting lexical representation is shared across speech tasks that demand different outputs, forming an abstract, output-independent code, or is instead specific to a speech task's processing network. To address this question, we recorded stereoelectroencephalography/electrocorticography from 26 neurosurgical patients (13 female, mean age = 30.1), being clinically monitored for epilepsy. Each participant heard 82 words and pseudowords, each presented twice, under three tasks differing in output: lexical decision (button press), repetition (overt speech), and passive listening. Lexical status (word vs. pseudoword) and phonemes were decoded from high-gamma activity (70-200 Hz - HG) using principal component analysis and linear support vector machine classifiers, with cross-task temporal generalization and cluster-based permutation testing. Phonetic information was decodable early in all three conditions. Lexical status was decodable during both decision and repetition tasks, peaking after stimulus offset, but was absent during passive listening. In contrast, phonetic decoding was present in all three conditions and occurred earlier, suggesting hierarchical processing in time. Classifiers trained on one active task generalized to the other (i.e. repeat ↔ decision), revealing an output-independent representation. Non-negative matrix factorization performed on HG activations recovered a temporal-cortex-dominated network that was shared across both tasks and distinguished words from pseudowords; networks in frontoparietal regions diverged by

output modality. Taken together, these results support a three-stage account of spoken-word processing: stimulus-driven acoustic-phonetic analysis present across conditions; a task-shared, output-independent lexical representation that evolves dynamically in temporal cortex, and later task-specific frontoparietal readouts (decision/articulation) that are also sensitive to lexical status. This evidence supports a model in which the brain represents lexical status in both shared and task-specific networks to guide behavior.

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Title: Pre-speech high-gamma activity tracks category, typicality, and embedding-derived semantic geometries during overt word production

Authors: *S. ROH[1], C. CHUNG[2];
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Abstract: Transformer-based language models provide continuous vector representations of meaning, but it remains unclear what kind of semantic structure is represented where and when before overt speech. Pre-speech activity may reflect multiple aspects of semantic organization, including category membership, graded position within a category, and continuous semantic similarity across words. To examine how these complementary forms of semantic structure are represented before articulation, we analyzed intracranial EEG recordings from 13 native Korean-speaking epilepsy patients performing an overt visual word-reading task with 108 Korean words and short predicative expressions. The task required no explicit semantic or typicality judgment. High-gamma activity (70-150 Hz) was analyzed during the 0-500 ms interval after visual word presentation, before the earliest retained speech onset. Semantic representational dissimilarity matrices were constructed from Korean Sentence-BERT embeddings. Hierarchical clustering yielded 10 interpretable semantic clusters, with higher within-cluster than between-cluster similarity. The embedding model captured continuous pairwise semantic distance, the cluster model captured embedding-derived category membership, and the typicality model captured each item's prototype-distance profile, defined by its distances to the centroid of its assigned cluster and to the centroids of other clusters. Representational similarity analysis showed that all three semantic geometries were detectable before articulation, but with distinct spatiotemporal profiles. Cluster-related structure was strongest in right superior temporal gyrus, emerging

around 120 ms. Prototype-relative typicality appeared in right frontal and temporal regions, including early effects in right dorsolateral prefrontal cortex and inferior frontal gyrus around 90-100 ms. Continuous embedding geometry showed a more left temporal/frontal profile, with effects in left superior temporal gyrus early and later effects in left temporal pole and dorsolateral prefrontal cortex. Direct model comparisons further indicated region-specific model dominance rather than a single global sequence from category to typicality to embedding. These findings suggest that pre-speech high-gamma activity contains multiple distinguishable components of semantic geometry. Category membership, prototype-relative position, and continuous embedding similarity may follow partially distinct regional trajectories that jointly contribute to semantic preparation for speech.

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Poster

PSTR079: Language: Neural Circuits and Mechanisms I

Location: WCC Halls A-C

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Program #/Poster #: PSTR079.19/LL26

Topic: A.07. Development of Neural Systems

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Title: Spatio-temporal dynamics of acoustic, phonetic and lexical speech encoding in the developing brain

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Abstract: Typically developing children acquire language rapidly; this process extends into young adulthood and relies on a distributed brain network linking speech sounds to meaning. Children with epilepsy show lower verbal comprehension, with on average greater seizure burden associated with greater impact on language. Which language subprocesses, acoustic, phonetic, or lexical, are affected and how, remains unclear, partly because we lack a full characterization of how the developing brain encodes speech across these levels. We recorded intracranial EEG from 101 children with epilepsy (ages 3-23; 13k channels) listening to 3 minutes of natural speech. Stimuli were annotated with acoustic (peak rate), phonetic (voicing,

manner/place of articulation, roundness), and lexical (phoneme surprisal and entropy) features. Neural responses were modeled using the multivariate temporal response function (mTRF) framework and time-resolved decoding analysis. Speech encoding was robust across participants and localized to a bilateral temporal-frontal-parietal network. Phonetic and lexical features showed overall stronger unique encoding than the acoustic features, with the acoustic features outperforming lexical features only in right STG. TRF peak latencies revealed a temporal hierarchy: lexical features peaked later (205 ms) than acoustic (187 ms) or phonetic (185 ms) features. Adolescents and young adults (ages 16-23) encoded lexical surprisal ~50 ms earlier than younger individuals. In sum, these findings reveal a bilateral temporal-frontal-parietal network underlying hierarchical speech encoding in the developing brain, with acoustic, phonetic, and lexical features engaging partially dissociable regions at distinct latencies. Lexical encoding was modulated by age. The absence of epilepsy-related effects (i.e., verbal comprehension scores and duration of seizure burden) may be due to limited statistical power. Future work should examine semantic and syntactic features to determine whether these findings extend to higher-order language processing.

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